(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 061 187**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **20.08.86**

(21) Application number: **82102330.6**

(22) Date of filing: **22.03.82**

(51) Int. Cl.⁴: **C 07 D 513/04**, A 61 K 31/425
// C07D209/48, C07D417/06,
(C07D513/04, 277:00, 223:00)

(54) **Bicyclic lactams as antihypertensives.**

(30) Priority: **23.03.81 US 246492**
19.02.82 US 348811

(43) Date of publication of application:
29.09.82 Bulletin 82/39

(45) Publication of the grant of the patent:
20.08.86 Bulletin 86/34

(84) Designated Contracting States:
CH DE FR GB IT LI NL

(56) References cited:
US-A-3 334 091

THE JOURNAL OF ORGANIC CHEMISTRY, vol. 45, no. 24, 21st November 1980, pages 5008-9; A.G. SCHULTZ: "On the intramolecular reactivity of azidoenones"

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EP 0 061 187 B1

Courier Press, Leamington Spa, England.

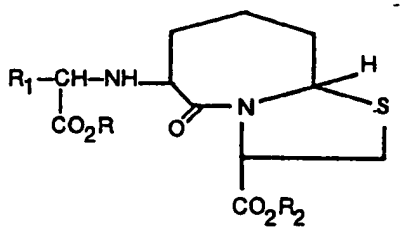
Description

The invention r lates t a specific bicyclic lactams which are useful as converting enzyme inhibitors and as antihypertensives.

US—A—3 334 091 describes specific bicyclic lactams having CNS (central nerv us system) activity but which are different from the compounds of the present invention. A pointer to an antihypertensive activity of those known lactams is not contained in that reference.

Description is given in J. Org. Chem., 1980, *45*, p. 5008—5009, of the preparation of specific bicyclic lactams which are different from the compounds of the present invention. Statements about a pharmacological activity off these known lactams are not contained in that reference.

The compounds of the invention are represented by the following formula (I)



(I)

wherein:

R and R_2 are independently hydrogen, C_{1-6} alkyl, phenyl, naphthyl, biphenyl and correesponding aralkyls having 1—6 carbon atoms in the alkyl moeity,

R_1 is hydrogen; alkyl having 1 to 12 carbon atoms, cycloalkyl having up to 12 carbon atoms, alkenyl having up to 12 carbon atoms and alkynyl having up to 12 carbon carbon atoms; C_{1-6} alkyl substituted by halo, hydroxy, carboxy, C_{1-6}-alkylthio, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, phenyl-, naphthyl- or biphenyl-C_{1-6}-alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6}-alkyl)amino, or C_{1-6} alkanoylamino or aroylamino; a residue having the formula $R^A(CH_2)_n$—Q—$(CH_2)_m$ wherein n is 0—2, m is 1—3, R^A is phenyl, naphthyl, biphenyl, indolyl, thienyl, imidazolyl, furyl, benzimidazolyl, pyridyl, quinolinyl, isoquilinyl, or benzothienyl whereby the aryl and heteroaryl moieties are optionally substituted by amino, di(C_{1-6}-alkyl)amino, C_{1-6}-alkyl-amino, hydroxy, hydroxy-C_{1-6}-alkyl, amino-C_{1-6}-alkyl, trihalo-C_{1-6}-alkyl, cyano, nitro, sulfonamido, aroyl, C_{1-6} alkyl, 1 or 2 halogens and C_{1-6} alkoxy and Q is O, S, N—R^B, —$CONR^C$—, —NR^CCO— or —CH=CH— wherein R^B is hydrogen, C_{1-6} alkyl, phenyl, naphthyl, biphenyl, aralkyl having 1 to 6 carbon atoms in the alkyl and "ar" defining phenyl, naphthyl or biphenyl, C_{1-6} alkanoyl or aroyl, and R^C is hydrogen or C_{1-6} alkyl; phenyl, naphthyl or biphenyl wherein the aryls can be substituted by C_{1-6} alkyl, amino-C_{1-6}-alkyl, C_{1-6} alkoxy, phenyl-, naphthyl- or biphenyloxy, aroyl, hydroxy, 1 ot 2 halogens; aralkyl or heteroaralkyl wherein the alkyl portion contains 1 to 6 carbon atoms and the aryl and heteroaryl moiety is defined as for R^A whereby the C_{1-6} group can be substituted by amino C_{1-6} alkanoylamino, aroylamino or hydroxyl and the aryl and heteroaryl groups can be substituted by 1 or 2 halogens, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, phenyl-, naphthyl- or biphenyloxy, aroyl, phenyl-, naphthyl- or biphenylthio, amino, amino-C_{1-6}-alkyl, C_{1-6} alkanoyl amino, aroylamino, di-C_{1-6}-alkylamino, C_{1-6} alkylamino, hydroxy, hydroxy-C_{1-6}-alkyl, trihalo-C_{1-6}-alkyl, nitro, cyano, or sulfonamido;

and the pharmaceutically acceptable salts thereof.

The lower alkyl groups, except where noted otherwise, represented by any of the variables include straight and branched chain hydrocarbon radicals from one to six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl: Examples of alkenyl residues are vinyl, allyl, butenyl and the like. The aralkyl and heteroaralkyl groups represented by any of the above variables include for example benzyl, phenethyl, 3,3-diphenylpropyl and 3-indolylmethyl. Halo means chloro, bromo, iodo or fluor. Aroyl includes benzoyl and 1-naphthoyl. Heteroaryl represents indolyl, thienyl, imidazolyl, furyl, benzimidazolyl, pyridyl, quinolinyl, isoquinolinyl, and benzothienyl. C_{1-6} alkanoylamino and aroylamino include, for example, acetylamino, and benzoylamino.

Preferred are those compounds of formula (I) wherein:

R and R_2 are as defined above; and

R_1 is alkyl having 1—10 carbon atoms, cycloalkyl having up to 10 carbon atoms, alkenyl having up to 10 carbon atoms and alkynyl having up to 10 carbon atoms; C_{1-6} alkyl substituted hydroxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6}-alkyl)amino, and C_{1-6} alkanoylamino or aroylamino; a residue having the formula $R^A(CH_2)_n$—Q—$(CH_2)_m$— wherein n is 0—2, m is 1—3, R^A is aryl or heteroaryl as defined above whereby the aryl and heteroaryl moieties are optionally substituted by C_{1-6} alkyl, 1 or 2 halogens, amino, cyano, hydroxy, or C_{1-6} alkoxy, and Q is =O, =S, =N—R^B, —$CONR^C$—, —NR^CCO—, or —CH=CH— wherein R^B is hydrogen, C_{1-6} alkyl, aralkyl as defined above, C_{1-6} alkanoyl, or aroyl and R^C is hydrogen or C_{1-6} alkyl; aralkyl or heteroaralkyl as defined above whereby the C_{1-6} alkyl groups can b substituted by amino, C_{1-6} alkan ylamin , ar ylamin or hydroxy and the aryl and heteroaryl groups can be substituted by C_{1-6} alkyl, 1 r 2 hal g ns, amino, cyano, hydroxy, C_{1-6} alk xy, amin -C_{1-6}-alkyl, or hydroxy-C_{1-6}-alkyl.

Still more prefered are those compounds of formula (I) wherein:

R and R_2 are as defined above;

R_1 is alkyl of 1—10 carb n atoms; C_{1-6} alkyl substituted by amino, C_{1-6} alkanoylamino, aroylamino, or C_{1-6} alkylthio; a residue having the formula $R^A(CH_2)_n—Q—(CH_2)_m—$ wherein n is 0—1, m is 1—2, R^A is phenyl optionally substituted by 1 or 2 halogens, C_{1-6} alkoxy, or cyano, and Q is O or S; aralkyl or heteroalkyl as defined above whereby the aryl and heteroaryl m ieties are optionally substituted by 1 r 2 halogens, cyano, hydroxy, hydroxy-C_{1-6} alkyl, amino, and amino-C_{1-6}-alkyl.

Most preferred are compounds of formula (I) wherein:

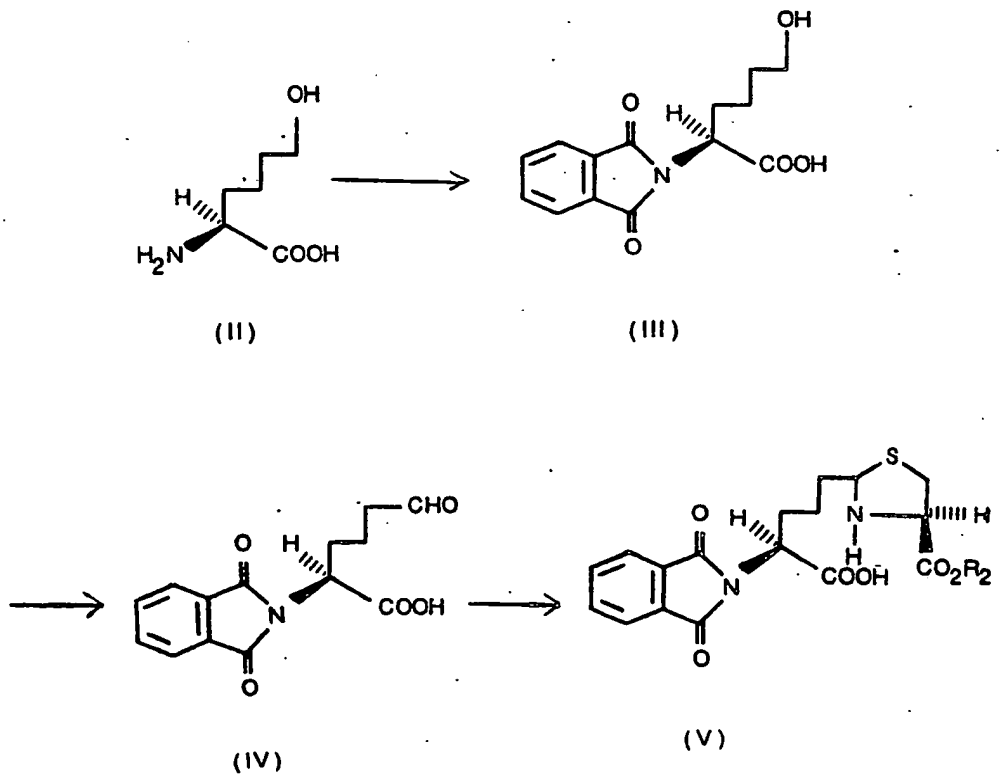
R and R_2 are independently hydrogen, C_{1-4} alkyl, phenyl, or benzyl; and,

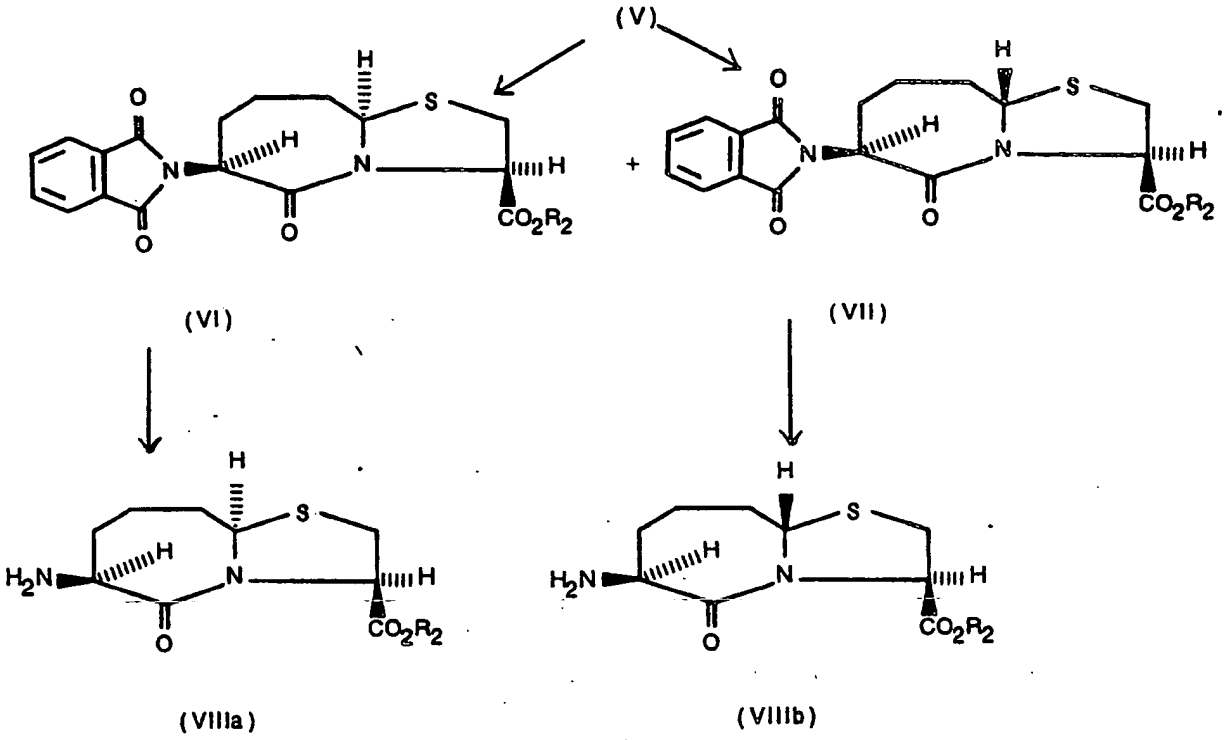
R_1 is alkyl of 1—8 carbon atoms; C_{1-6}-alkyl substituted by amino or C_{1-6} alkylthio; a residue having the formula $R^A(CH_2)_n—Q—(CH_2)_m—$ wherein n is 0, m is 1, LR^A is phenyl, and Q is O or S; aralkyl wherein the aryl is phenyl or naphthyl and the alkyl group contains 1 to 3 carbon atoms, or heteroaralkyl wherein the heteroaryl group is indole, thiophene, imidazole, pyridine, quinoline or isoquinoline and the alkyl group contains 1 to 3 carbon atoms; substituted aralkyl wherein the aryl is a phenyl group, the alkyl contains 1 to 3 carbon atoms, and the phenyl substitutents can be halogen, hydroxy, phenoxy, C_{1-6} alkoxy, amino, or aminomethyl.

The preferred, more preferred and most preferred compounds also include the pharmaceutically acceptable salts thereof.

The products of Formula (I) can be produced from bicyclic intermediate (VIII) and from the separated, preferred diastereomers of (VIII); i.e., (VIIIa) and (VIIIb). The synthesis of compound (VIII) can be conducted from, for example, 2(S)-amino-6-hydroxyhexanoic acid (II) as shown in Reaction Scheme I below wherein R_2 is as defined above.

REACTION SCHEME I



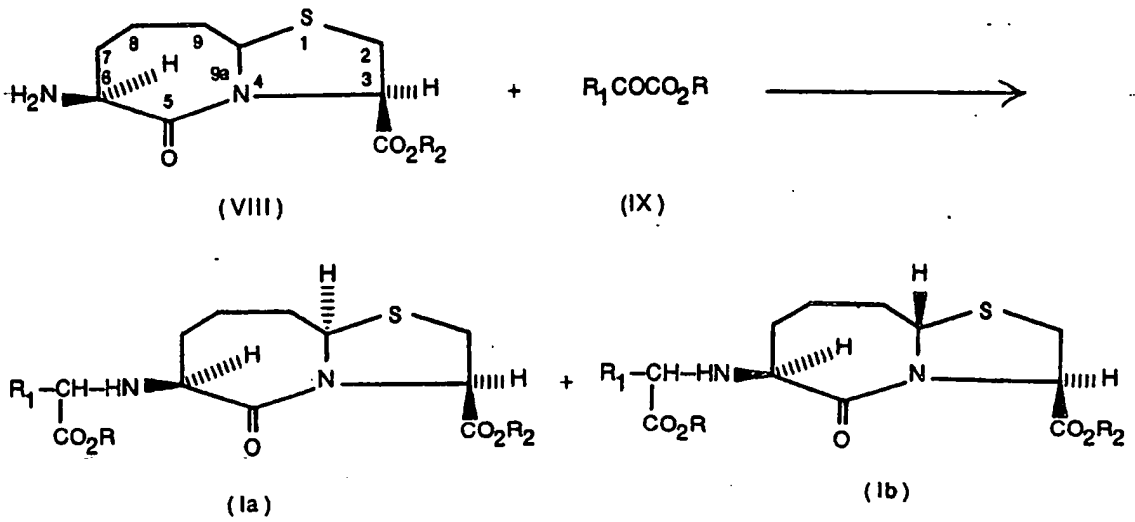


As shown in Reaction Scheme (I) above, known starting material (II) is protected as the phthalimido derivative (III) and oxidized with pyridinium dichromate to the aldehyde, 5-formyl-2(S)-phthalimido-pentanoic acid (IV). Condensation with an ester of R-cysteine yields a diastereomeric mixture of thiazolidines (V) which, upon treatment with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, undergo ring closure to form S, R, R(VI) and S, S, R(VII) methyl 6-phehalimidooctahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate. The isomers are separated by liquid chromatography and are deprotected by treatment with hydrazine to yield aminoesters (VIIIa) and (VIIIb). The ester group can then be removed with dilute alkali to yield the acids (R_2=H) of (VIIIa) and (VIIIb).

As summarized in Reaction Scheme (II) below, products of Formula (I) can be prepared from the diastereomeric mixture of amino cyclic lactams (VIII) or from diastereomerically pure compounds (VIIIa) and (VIIIb) by reductive alkylation of these intermediates with α-keto acids or α-keto esters (IX). In these alkylations, one typically uses sodium cyanoborohydride under neutral conditions, but it is also possible to employ hydrides bearing optically active ligands or sterically bulky ligands selected to improve the sterochemical control in these reductions. Alternatively, the reductive alkylations can be achieved by catalytic hydrogenation over 10% palladium on carbon or other suitable catalysts.

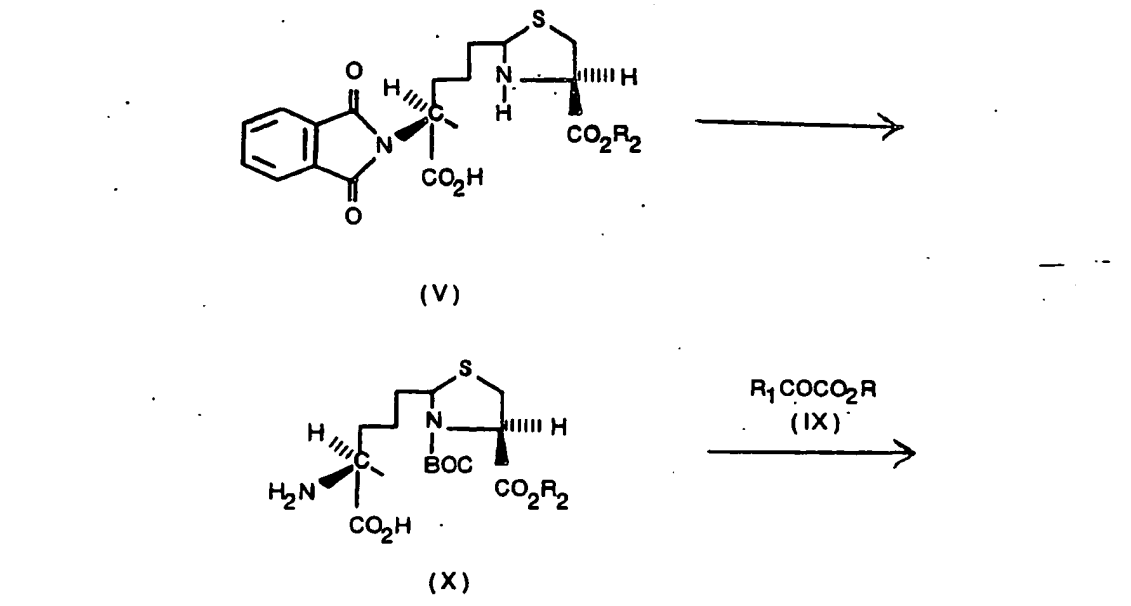
The final stages in these syntheses are to separate the desired diastereomers by chromatography or crystallization and to remove protecting groups, if present, by standard means. When identical diesters of Formula (I) are desired, they can be prepared from, for example, diacids of I($R=R_2$=H) using the desired alcohols under anhydrous acidic conditions.

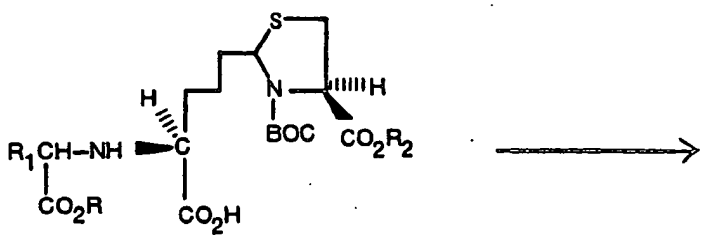
REACTION SCHEME II



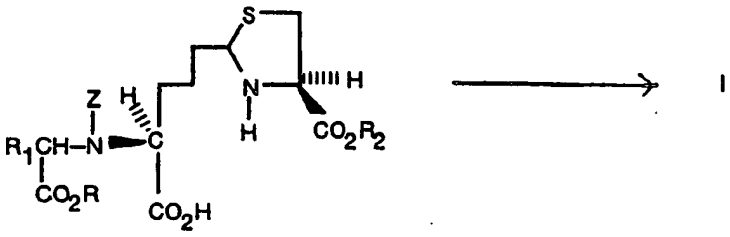
In Reaction Scheme (III) which follows, an alternate route to compounds of Formula (I) is shown which involves a variation in the sequence of the reactions utilized in Reaction Schemes (I) and (II). In Reaction Scheme (III), the reductive alkylation using (IX) is performed on intermediate (X) followed by ring closure of intermediate (XII) to yield products of Formula (I) after chromatography and removal of protecting groups. In this sequence, R, R_1 and R_2 are as defined above (except R, R_2H) and Z is optionally hydrogen or a suitable protecting functionality such as, for example, the formyl group. The ring forming and reductive alkylation reactions are performed under substantially the same conditions as utilized in and described above for Reactions Schemes (I) and (II).

REACTION SCHEME III





(XI)



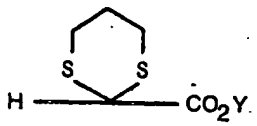
(XII)

Intermediate (VIII) has three asymmetric carbon atoms: one bears the NH_2 group; another is that bearing the hydrogen at the ring juncture; and, a third is that bearing the CO_2R_2 group. The preferred absolute configuration at these centers are 6(S), 9a(R), 3(R)(VIIIa) and 6(S), 9a(S), 3(R)(VIIIb).

In Formula (I)-compounds, the carbon atom bearing R_1 is also asymmetric (R_1H). Both isomers in this position have some biological activity, although the natural L-aminoacid configuration is preferred. In most cases, the absolute configuration at this center is designated (S).

Preferred diastereomers are isolated by chromatography or crystallization of intermediates or the end products of their salts. One can also resolve intermediates by the use of optically active salts or bases. Finally, if desired, compounds of this invention can also be employed as a mixture of their enantiomers or diastereomers.

The α-keto acids and α-keto esters (IX) utilized in the process of the invention are known in the art or can be made by numerous, known methods. For example, synthons such as



can be converted to α-keto acids or esters having methods involving alkylation followed by hydrolysis as described in the literature. An excellent method involves the raction of Grignard reagents R_1MgX with $ClCOCO_2Y$ or YO_2CCO_2Y. Another method involves condensing substituted acetic acid esters with diethyl oxalate followed by hydrolytic decarboxylation under acidic conditions to obtain α-keto acids. Carefully controlled acid hydrolysis in alcohol of acyl cyanides, which are prepared from acid chlorides and cuprous cyanide, also proves to be a viable synthetic route to α-keto esters. Nucleophilic displacement reactions on chloro or bromo pyvuric acid (ester) can also be used to produce a variety of interesting α-keto acids (esters). In these formulae, y is a group such as loweralkyl or benzyl and protecting groups are employed as necessary in the R_1 group if interfering functionality is present.

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine and the like. Also salts with organic and inorganic acids may be prepared, e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

The salts may be formed by conventional means as by reacting the free acid or free base forms f the product wiht one r more quivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then r m ved *in vacuo* or by fr ez -drying or by xchanging the cations of an existing salt for another cation on a suitable i n xchang resin.

The compounds f this invention inhibit angiotensin converting enzyme and thus block conversion of the decapeptide angiot nsin I to angiotensin II. Anti tensin II is a potent pressor substance. Thus, blood-pressure lowering can result from inhibition of its biosynthesis especially in animals and humans whose hypertension is angiotensin II related. Furthermore, c nv rting enzyme degrad s the vasodepressor substance, bradykinin. Theref re, inhibit rs of angiotensin c nv rting enzyme may lower bl d-pressure also by potentiation of bradykinin. Although the realtive importance of these and other possible mechanisms remains to be established, inhibitors of angiotensin converting enzyme are effective antihypertensive agents in a variety of animal models and are useful clinically, for example, in many human patients with renovascular, malignant and essential hypertension. See, for example, D. W. Cushman et al., *Biochemistry 16, 5484 (1977).*

The evaluation of converting enzyme inhibitors is guided by *in vitro* enzyme inhibition assays. For example, a useful method is that of Y. Piquilloid, A. Reinharz and M. Roth, *Biochem. Biophys. Acta, 206,* 136 (1970) in which the hydrolysis of carbobenzyloxyphenylalanylhistidinylleucine is measured. *In vivo* evaluations may be made, for example, in normotensive rats challenged with angiotensin I by the technique of J. R. Weeks and J. A. Jones, *Proc. Soc. Exp. Biol. Med., 104,* 646 (1960) or in a high renin rat model such as that of S. Koletsky et al., *Proc. Soc. Exp. Biol. Med. 125,* 96 (1967).

Thus, the compounds of this invention are useful as antihypertensives in treating hypertensive mammals, including humans, and they can be utilized to achieve the reduction of blood pressure by formulating in compositions such as tablets, capsules or elixers for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients in need of such treatment in a dosage range of 0.5 to 100 mg per patient generally given several times, thus giving a total daily dose of from 0.5 to 400 mg per day. The dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

It is often advantageous to administer compounds of this invention in combination with other antihypertensives and/or diuretics. For example, the compounds of this invention can be given in combination with such compounds as amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetate and cryptenamine tannates, deserpidine, diazoxide, ethacrynic acid, furosemide, guanethidene sulfate, hydralazine hydrochloride, hydrochlorothiazide, hydroflumethiazide, metalazone, metoprolol tartrate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, (S)-1-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-3-{[4-(2-thienyl)-1H-imidazol-2-yl]phenoxy}-2-propanol, polythiazide, the pivaloyloxyethyl ester of methyldopa, indacrinone and variable ratios of its enantiomers, nifedipine, verapamil, diltiazam, flumethiazide, bendroflumethiazide, atenolol, (+)-4-{3-{-[2-(1-hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl}propyl}benzoic acid, bumetanide, pyrazosin, propanolol, *rauwolfia serpentina,* rescinnamine, reserpine, spironolactone, trimolol, trichlormethiazide, benzthiazide, quinethazone, tricrynafan, triamterene, acetazolamide, aminophylline, cyclothiaxide and merethoxylline procaine, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, one of the antihypertensives of this invention effective clinically in the 0.5—100 milligrams per day range can be effectively combined at levels at the 0.1—100 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (10—100 mg), timilol (5—60 g), methyldopa (65—2000 mg), the pivaloyloxyethyl ester of methyldopa (30—1000 mg), indacrinone and variable ratios of its enentiomers (25—150 mg) and (+)-4-{3-{[2-(1-(hydroxy-cyclohexyl)ethyl]-4-oxo-2-thiaxolidinyl}propyl}-benzoic acid (10—100 mg).

In addition, the triple drug combinations of hydrochlorothiazide (10—100 mg) plus timolol (5—60 mg) plus converting enzyme inhibitor of this invention (0.5—100 m g) of hydrochlorothiazide (10—100 mg) plus amiloride (5—20 mg) plus converting enzyme inhibitor of this invention (0.5—100 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors. Typically, the combinations shown above are formulated into pharmaceutical compositions as discussed below.

0.1 to 50 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations in such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules, and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and th like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, il of wintergreen or cherry. When th dosage unit form is a capsule, it may c ntain, in addition to materials of th above typ , a liquid carrier such as fatty oil. Various other

materials may b present as coatings or to otherwis modify the physical f rm of th d sag unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixer may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as pr servatives, a dye and a flavoring such as cherry or orange flavour.

Sterile compositi ns for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, or a synthetic fatty vehicle like ethyl oleate. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples are illustrative of the invention and constitute especially preferred embodiments. The preferred diastereomers of these examples are isolated by conventional column chromatography or fractional crystallization. Unless otherwise indicated, all temperatures are in degrees Celsius.

Examples 1—7 refer to starting compounds. Examples 8, 18, 21, 36, 39, 40, 46 and 48 refer to intermediates. Examples 9—17, 19, 20, 22—35, 37, 38, 41—45, 47, 49 and 50 refer to the desired final products.

Example 1

6-Hydroxy-2(S)-phthalimidohexanoic Acid

Sodium carbonate (4.82 g) and 2(S)-amino-6-hydroxyhexanoic acid (6.70 g) were dissolved in 70 ml of water and treated with 9.98 g of N-carbethoxyphthalidmide. The mixture was stirred for 1.5 hours and then filtered to remove unreacted N-carbethoxyphthalimide. The filtrate was cooled and acidified with 6N HCl. The white precipitate (10.6 g) was isolated by filtration and recrystallized from water to give fine needles, m.p. 162—163; $[\alpha]_D^{25°} = -36.3°$ (MeOH, c = 2.0). Tlc on silica (4:1 ethyl acetate:acetic acid) indicated a single spot, $R_f = 0.67$. The ^1H NMR spectrum (d_6-DMSO) shows a singlet at δ 7.90 (4H), triplets at δ 4.77 (1H, J=7.9Hz) and δ 3.36 (2H, J=6.0Hz), and multiplets centered at 2.15 (2H) and 1.40 (4H).

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.64, H, 5.46; N, 5.05
Found: C, 60.69; H, 5.44; N, 4.97

Example 2

5-Formyl-2(S)-phthalimidopentanoic acid

6-Hydroxy-2(S)-phthalimidohexanoic acid (1.94 g) was dissolved in 145 ml of CH_2Cl_2 containing 2.26 ml of pyridine. Pyridinium dichromate (1.95 g) was added and the mixture stirred overnight under nitrogen. By addition to 200 ml of ethyl acetate and filtration, chromium salts were removed. The filtrate was concentrated under vacuum. The residue was redissolved in 250 ml of ethyl acetate and the solution refiltered. The filtrate was finally passed through a $MgSO_4$ pad to remove trace amounts of chromium salts and concentrated to afford a white solid, 0.475 g; m.p. 219—22°C; $[\alpha]_D^{25°} = -41.6°$ (THF, c = 1.5). Tlc on silica (4:1 ethyl acetate:acetic acid) inidcated a single spot at $R_f = 0.79$. ^1H NMR spectrum (d_6-DMSO) showed triplets at δ 9.65 (1H) and δ 4.85 (1H, J=7.5Hz), a singlet at δ 7.95 (4H), and a broad multiplet at δ 0.9—2.50 (6H) ppm. ^{13}C NMR spectrum (d_6-DMSO) showed single absorptions at 202.9, 170.5, 167.5, 134.9, 131.3, 123.5, 51.7, 42.4, 27.8, and 18.7 ppm.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09
Found: C, 60.93; H, 5.05; N, 5.39

Example 3

Alternative Synthesis of 5-Formyl-2(S)-phthalimidopentanoic acid

6-Hydroxy-2(S)-phthalimidohexanoic acid (5.0 g) was dissolved in a mixture of 90 ml of methanol and 9 ml of water. To this solution, an aqueous 0.5M cesium carbonate solution (18 ml) was added and the mixture stirred for a few minutes. Most of the methanol was removed *in vacuo* and the resulting aqueous residue was freeze-dried. The lyophilized material was dissolved in DMF (70 ml) and treated with 3.08 g of benzyl bromide. After stirring under nitrogen for 6 hours, the reaction mixture was diluted with 450 ml of water and repeatedly extracted with ethyl acetate. Organic layers were then back-washed with water, dried (Na_2SO_4), and concentrated to give 6.58 g of benzyl 6-hydroxy-2(S)-phthalimidohexanoate. Recrystallization from ether gave a white solid, m.p. 106.5—108°; $[\alpha]_D^{25°} \doteq -27.6°$ (MeOH, c = 1.77).

Benzyl 6-hydroxy-2(S)-phthalimidohexanoate (4.0 g) was dissolved in CH_2Cl_2 and treated with pyridinium chlorochromate (3.64 g). The reaction mixture was stirred under nitrogen for 4 hours and then diluted with 160 ml of ether. The mixture was filtered through a celite pad and concentrated to give an oil. This oil was passed through a short florisil column with ether as eluent. Concentration and drying *in vacuo* yielded pure benzyl 5-formyl-2(S)-phthalimidopentanoate (3.16 g); $[\alpha]_D^{25°} = -18.6°$ (CH_2Cl_2, c = 4.1); I.R. (neat): 2730 cm^{-1}.

Benzyl 5-formyl-2(S)-phthalimidopentanoate :4.72 g) was dissolved in 230 ml of ethyl acetate and hydrogenated at 5 psig of hydrogen over 0.82 g of 10% palladium on carbon. After th uptake of 1 equivalent of hydrogen, catalyst was removed by filtration. Removal of solvent afforded 3.64 g of 5-formyl-2(S)-phthalimidopentanoic acid.

Example 4

Methyl 2-(4'-carboxy-4'-phthalimidobutyl)-4(R)-thiazolidinecarboxylate

A s luti n of L-cysteine methyl ester (1.71 g) and 5-formyl-2(S)-phthalimidopentanoic acid (3.49 g) in 120 ml of tetrahydrofuran was stirred under nitrogen for 2.5 hours and then taken to dryness to yield a white foam. This residue was dissolved in 250 ml of chlorofrm and washed with water (2 × 30 ml). The combined aqueous layers were back extracted with chloroform (2 × 30 ml). The organic layers were dried (Na_2SO_4) and then concentrated *in vacuo* to give a white foam, 4.83 g. Tlc on silica [4:1 Ethyl acetate:acetic acid] indicated a major spot at R_f = 0.72. Exact mass measurement showed a molecular ion at 392.1024 (calcd. 392.1041). 'H NMR spectrum ($CDCl_3$) showed a multiplet at δ 7.72 (4H) and a singlet at δ 3.78 (3H).

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$-1/2H_2O: C, 53.85; H, 5.27; N, 6.98; S, 7.99
Found: C, 54.00; H, 5.30; N, 6.58; S, 7.61

Example 5

Methyl [3*R*-(3α,6α9aα)]-6-phthalimidooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate and methyl [3*R*-(3α,6α9aβ)]-6-phthalimidooctahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylate

The mixture of diastereomatic thiazolidines (6.77 mg) obtained in Example 4 and 469 mg of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) were dissolved in 30 ml of tetrahydrofuran and stirred at room temperature overnight under nitrogen. Concentration afforded a clear residue which was dissolved in 175 ml of ethyl acetate and washed with dilute hydrochloric acid (0.5N), 5% sodium bicarbonate solution, water, and brine. The residue, after drying with Na_2SO_4, was chromatographed on silica gel (eluant 1:1 ethyl acetate:hexane) to afford a mixture of isomers, wt. 348 mg. The diasteromers were separated on a Whatman ODS-3 reverse phase column using a 70:30 water-acetonitrole mixture as eluant.

The first component eluted from the column was methyl [3*R*-(3α-6α;9aα)-6-phthalimidooctahydro-5-oxothiazolo-[3,2-*a*]azepine-3-carboxylate (9a(S)isomer), 141 mg. Recrystallization from ethyl acetate/hexane afforded fine white needles, m.p. 159.5—61°; $[\alpha]_D^{25°}$ = −202.1 ($CHCl_3$); 300 MHz 'HNMR ($CDCl_3$) δ 1.99 (m, 3H), 2.29 (m, 2H), 2.94 (m, 1H), 3.27 (1/2ABq, J_{AB}=12Hz, ΔV_{AB} = 34, J_{AX}=7Hz, 1H), 3.16 (1/2ABq, J_{AB}=12Hz, ΔV_{AB} = 34, J_{BX}=7Hz, 1H), 3.75 (s, 3H), 5.01 (d, *J*=12Hz, 1H), 5.21 (t, *J*=7Hz, 1H), 5.27 (dd, *J*=9.5Hz, J=4Hz, 1H), 7.75 (m, 2H), 7.88 (m, 2H); I.R. (KBr): 1710 and 1650 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.84; N, 7.48; S, 8.57
Found: C, 57,70; H, 4.87; N, 7.41; S, 8.45

The second component eluted from the column was methyl [3*R*-(3α,6α,9aβ)]-6-phthalimidooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (9a(R)isomer, configuration deterined by X-ray analysis), 177 mg. Recrystallization from ethyl acetate/hexane produced fine needles, m.p. 157—157.5°; $[\alpha]_D^{25°}$ = −32.2 ($CHCl_3$); 300 MHz 'H NMR ($CDCl_3$) δ 1.75—2.26 (m, 5H), 2.85 (q, *J*=12Hz, 1H)), 3.22 (1/2ABq, J_{AB}=12Hz, ΔV_{AB} = 21.7; J_{AX}=6.5Hz, 1H), 3.29 (1/2ABq. J_{AB}=12Hz, ΔV_{AB} = 21.7; J_{BX}=2Hz, 1H), 3.79 (s, 3H), 4.99 (d, *J*=12Hz, 1H), 5.15 (d, *J*=10Hx, 1H), 5.34 (dd, J_{AX}=6.5Hz, J_{BX}=2Hz, 1H), 7.74 (m, 2H), 7.87 (m, 2H); I.R. (KBr): 1750, 1710, and 1640 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.84; N, 7.48; S, 8.57
Found: C, 58.04; H, 4.90; N, 7.43; S, 8.62

Example 6

Ethyl [3*R*-(3α,6α,9aα)]-6-phthalimidooctahydro-5-oxothiazolo-[3,2-*a*]azepine-3-carboxylate and ethyl [3*R*-[3α,6α,9aβ)]-6-phthalimidooctahydro-5-oxo-thiazolo[3,2-*a*)-azepine-3-carboxylate

A solution of L-cysteine ethyl ester (0.205 g) and 5-formyl-2(S)-phthalimidopentanoic acid (0.379 g) in 10 ml of dry tetrahydrofuran was stirred for 2 hours under nitrogen. Concentration of the reaction mixture yielded a foam. This residue was dissolved in 150 ml of chloroform and washed with water (2 × 25 ml). The aqueous layers were back-washed with chloroform (2 × 25 mlk). The organic layers were dried and then concentrated under reduced pressure to give a white foam, 0.554 g. Tlc on silica [4:1 ethyl acetate:acetic acid] indicated a major spot at R_f = 0.80. This thiazolidine was dissolved in dry tetrahydrofuran (15 ml) and treated with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). The reaction mixture was stirred for four days under nitrogen. Concentration afforded an oil which was dissolved in 150 ml of ethyl acetate and washed with 0.5N hydrochloric acid, 5% sodium bicarbonate solution, water, and brine. After drying with Na_2SO_4, the product (0.681 g) was chromatographed on silical gel (3:2 Hexane:ethyl acetate, R_f = 0.26) to afford a mixture of diasteromers, wt. 0.294 g. HPLC analysis (reverse phase) indicated a 50:50 mixture of isomers. The mass spectrum showed a molecular ion at 388 m/e. 'H NMR (200MHz, $CDCl_3$) δ 1.28 (t, *J*=7Hz) 1.32 (t, *J*=7Hz) [3H], 1.68—2.40 (m, 5H), 2.82 (m, 1H), 3.20 (m, 2H), 4.19 (m, 2H), 3.94 (d, *J*=12Hz) 5.06—5.30 (m) [3H], 7.66 (m, 2H), 7.79 (m, 2H). Diastereomers can be separated by chromatography.

Example 7

Methyl [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate hydrochloride

Methyl [3*R*-(3α,6α,9aβ)]-6-phthalimido-octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (259 mg) was dissolved in 15 ml of absolute ethanol with gentle heating. Hydrazine hydrate (0.037 ml) was added and the mixture stirred at room temperature for 4 days under nitrogen. After concentration under vacuum t dryness, the residue was treated with 20 ml of 0.5M HCl at 0° for 3 hours. Th precipitated phthalhydrazide was filtered off and the filtrate freeze-dried to yield 220 mg of product. Tlc on silica (1:1:1:1 ethyl

acetate:n-butanol:water:acetic acid) indicated a single spot by ninhydrin, R_f = 0.63. 'H NMR (200 Mhz, CD_3OD) δ 1.8—2.18 (m, 6H), 3.30 (2H), 3.77 (s, 3H), 4.26 (d, *J*=9Hz, 1H), 5.17 (dd, *J*=7Hz, J=3.5Hz, 1H), 5.25 (t, *J*=4.5Hz, 1H); exact mass measur ment (free base), Obs. 244.0878, calcd, 244.0881.

Example 8

[3*R*-(3α,6α,9aβ)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*azepine-3-carboxylic acid

Methyl [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*azepine-3-carboxyllate (220 mg) was dissolved in 5 ml of CH_3OH and treated with 4.3 ml of 1M NaOH at room temperature overnight. The reaction mixture was absorbed on 15 ml of strong acid ion-exchange resin and eluted with 3% pyridine in water to yield 133 mg of product. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single spot at R_f = 0.56. Recrystallized from methanol, m.p. 208—210°(dec); $[\alpha]_D^{25°}$ = −84.5° (c = 1.58, 1N HCl); 'H NMR (200 MHz, D_2O) δ 2.02 (m, 6H), 3.27 (d, *J*=5Hz, 2H), 4.32 (m, 1H), 4.97 (t, *J*=5Hz, 1H), 5.16 (m, 1H).

Anal. Calcd. for $C_9H_{14}N_2O_3S$: C, 46,94; H, 6.13; N, 12.17; S, 13.93
Found: C, 46.66; H, 6.34; N, 12.01; S, 13.69

Example 9

Methyl [3*R*-[3α,6α(*S***R**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

A solution of methyl [3*R*-[3α,6α,9aβ]]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate hydrochloride (414 mg) in aqueous methanol was adjusted to pH = 6.25 with 1M NaOH. The mixture was concentrated and then redissolved in absolute methanol (20 ml). Methyl 2-oxo-4-phenylbutyrate (1.42 g) and 3A powdered molecular sieves (4 g) were added. A solution of sodium cyanoborohydride (277 mg) in 4 ml of methanol was added via a syringe pump over 24 hours. When reaction was complete, the sieves were removed by filtration and the filtrate concentrated. The residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried and concentrated to dryness. The mixture of diastereomers was separated by silica gel chromatography with 1:1 hexane:ethyl acetate as eluant.

The first diastereomer (R_f = 0.23) eluted from the column was methyl [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-caboxylate, 177 mg; 'H NMR (200MHz, $CDCl_3$) δ 1.52—2.14 (m, 8H);, 2.71 (t, J=8Hz, 2H), 3.18 (m, 4H), 3.66 (s, 3H), 3.73 (s, 3H), 4.85 (d, J=9Hz, 1H), 5.27 (dd, J=7Hz, J=3Hz, 1H), 7.26 (m, 5H); exact measurement, obs. 420.1711, calcd. 420.1718; $[\alpha]_D^{25°}$ = −42.9° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66; S, 7.63
Found: C, 59.98; H, 6.76; N, 6.49; S, 7.35

The second diastereomer (R_f = 0.29) eluted from the column was methyl [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate, 290 mg; 'H NMR (200 MHz, $CDCl_3$) δ 1.62—2.24 (m, 8H), 2.74)t, *J*=8Hz, 2H), 3.14—3.46 (m, 4H), 3.73 (s, 3H), 3.80 (s, 3H), 4.99 (d, *J*=9Hz, 1H), 5.28 (dd, *J*=7Hz, *J*=3Hz, 1H), 7.28 (m, 5H); exact mass measurement, obs. 420.1711, calcd. 420.1718; I.R. 1730 and 1650 cm^{-1}; $[\alpha]_D^{25°}$ = −65.8° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66; S, 7.63
Found: C, 60.24; H, 6.80; N, 6.47; S, 7.57

Example 10

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

Methyl [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (180 mg) was dissolved in 2 ml of CH_3OH and 2 ml of 1M NaOH. After standing overnight, the product was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. Appropriate fraction was concentrated and dried *in vacuo* to afford a white solid, 165 mg. Recrystallized from methanol, m.p. 212—13° (dec); $[\alpha]_D^{25°}$ = −90.9° (0.1N NaOH, c = 0.2); I.R. (KBr) 1718 and 1654 cm^{-1}; Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single product, R_f = 0.78; 'H NMR (200 MHz, d_6-DMSO) δ 1.36—2.20 (m, —H), 2.69 (m, 2H), 3.24 (m, 3H), 3.81 (d, *J*=10Hz, 1H), 5.07 (dd, *J*=7Hz, *J*=3.5Hz, 1H) 5.19 (d, *J*=8Hz, 1H), 7.26 (m, 5H). The mass spectrum showed a molecular ion at 536 m /e for the disiylated species. X-ray crystal structure analysis established the stereochemistry of the side chain as (*S*).

Anal. Calcd. for $C_{19}H_{24}N_2O_5S{\cdot}1/2H_2O$: C, 56.84; H, 6.28; N, 6.98; S, 7.99
Found: C, 56.68; H, 6.11; N, 6.82; S, 7.87

Example 11

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

Methyl [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (100 mg) was dissolved in 1 ml of methanol and treated with 1 ml of 1M NaOH. Aft r standing v rnight, the product was absorbed on strong acid ion-exchange resin and elut d with 3% pyridine in H_2O. Concentration and drying afforded white s lid, 93 mg. R crystallized fr m

methanol, m.p. 250—51° (dec). Tlc on silica [1:1:1:1 ethyl acetate:n-butanol-water-acetic acid] indicated a single spot, R_f = 0.73. $[\alpha]_D^{25°}$ = −67.7° (0.1N NaOH, c = 0.2). 'H NMR (200MHz, CD_3OD) δ 1.68—2.36 (m, 8H), 2.75 (m, 2H), 3.24 (m, 2H), 3.68 (t, *J*=5Hz, 1H), 4.04 (d, *J*=10Hz, 1H), 5.04 (d, *J*=9Hz, 1H), 5.16 (dd, *J*=5Hz, *J*=3Hz, 1H), 7.24 (m, 5H). The mass spectrum showed a molecular i n at 536 m/e for th disilylated species.

Anal. Calcd. for $C_{19}H_{24}N_2O_5S$: C, 58.14; H, 6.16; N, 7.14; S, 8.17
Found: C, 57.95; H, 6.22; N, 6.98; S, 8.12

Example 12

[3*R*-[3α,6α(*S***R**),9aβ]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

[3*R*-[3α,6α9aβ)]-6-Aminooctahydro-5-oxo-thiazolo[3,2-*a*]azepine-3-carboxylic acid (83 mg) and 2-oxo-4-phenylbutyric acid (0.32 g) were suspended in 5 ml of H_2O and adjsuted to pH 6.0 with 1M NaOH. Sodium cyanoborohydride (45 mg) in 2 ml of H_2O was slowly added. When reaction was complete, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in H_2O to yield product, wt. 117 mg. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated two spots, R_f = 0.73 and 0.78. The mas spectrum showed a molecular ion at 536 m/e for the disilylated species. 'H NMR (60MHz, CD_3OD) δ 1.5—2.45 (m, 8H), 2.75 (m, 2H), 3.25 (m, 2H), 3.60 (m, 1H), 4.10 (m, 1H), 5.01 (m, 2H), 7.18 (s, 5H).

Example 13

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid and [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

A solution of [3*R*-(3α,6α,9aβ)]-6-amino-ocatahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (345 mg) in 10 ml of H_2O was adjusted to pH 6.3 with silute NaOH. The solution was then freeze dried. The residue and ethyl 2-oxo-4-phenylbutyrate (1.55 g) were partly dissolved in 25 ml of absolute ethanol. Powdered 3A molecular sieves (3.5 g) were added. To this mixture, a solution of sodium cyanoborohydride (282 mg) in 5 ml of ethanol was slowly added via a syringe pump. After completion of the reaction, the mixture was filtered and the filtrate taken to dryness. The residue was partitioned between water (100 ml) and ether (50 ml). The layers were separated. The aqueous layer was absorbed on strong acid ion-exchange resin and eluted with water, then 3% pyridine in water to yield to title product as a mixture of diastereomers, wt. 638 mg. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a major spot at R_f = 0.80. Diastereomers were separated by chromatography on Sephadex LH—20 (MeOH, 2.54 cm × 2 m).

The first diastereomer to elute from the column was [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid, wt. 338 mg; exact mass measurement, obs. 420.1715, calcd. 420.1718; 'H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, *J*=6Hz, 3H), 1.56—2.22 (m, 8H), 2.74 (t, *J*=8Hz, 2H), 3.18 (m, 1H), 3.42 (m, 3H), 3.77 (br s, 2H, exchangeable), 4.20 (m, 2H), 4.96 (d, *J*=8Hz, 1H), 5.19 (br s, 1H), 7.25 (m, 5H). ^{13}C NMR spectrum in $CDCl_3$/meOH (3:1) showed single absorptions at 174.5, 172.8, 141.4, 128.7, 126.3, 64.1, 62.9, 61.4,m 60.4, 60.3, 35.7, 34.9, 32.2, 31.9, 31.5, 28.3, and 14.4 ppm.

The second diastereomer to elute from the column was [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid, wt. 101 mg; exact mass measurement, obs. 420.1727, calcd. 420.1718; 'H NMR (200MHz, $CDCl_3$) δ 1.28 (t, *J*=7Hz, 3H), 1.54—2.22 (m, 8H), 2.77 (t, *J*=7Hz, 2H), 3.15 (m, 1H), 3.34 (m, 3H), 3.54 (br s, 2H, exchangeable), 4.19 (q, *J*=7Hz, 2H), 4.88 (d, *J*=7Hz, 1H), 5.24 (d, *J*=5Hz, 1H), 7.27 (m, 5H).

Example 14

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride

Anhydrous hydrogen chloride was bubbled into a solution of [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (320 mg) in ethyl aceetate (30 ml) at 0°. Precipitate was collected, wt. 305 mg; m.p. 224—25° (dec); $[\alpha]_D^{25°}$ = −38.5° (EtOH, c = 1.2); I.R. (KBr): 1730, 1690, and 1658 cm^{-1}; Tlc on silica [1:1:1:1 ethyl acetate: n-butanol:water:acetic acid] indicated in a single spot at R_f = 0.81.

Anal. Calcd. for $C_{21}H_{28}N_2O_5S$-HCL-1/2H_2O: C, 54.12; H, 6.49; N, 6.01; S, 6.68; Cl, 7.61
Found: C, 54.19; H, 6.47; S, 6.71; Cl, 7.85

Example 15

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride

Anhydrous hydrogen chloride was bubbled into a solution of [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-th xycarb nyl-3-phenylpropyl)amin]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (120 mg) in ethyl acetate (20 ml) at 0°. Precipitat was collected, wt. 122 mg; m.p. 123—25°; $[\alpha]_D^{25°}$ = −77.2° (EtOH,

c = 0.6); Tlc on silica [1:1:1:1 ethyl acetate: n-butanol:water:acetic acid] indicated a single spot at R_f = 0.85.

Anal. Calcd. f r $C_{21}H_{28}N_2O_5S$-HCl-0.25H_2O: C, 54.65; H, 6.44; N, 6.07; S, 6.95; Cl, 7.68
Found: C, 54.75; H. 6.40; N, 5.90; S, 6.83; Cl, 7.29

Example 16

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

A solution of [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride (147 mg) in 2.5 ml of methanol was treated with 1.6 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin. Elution with water and then 4% pyridine in water permitted recovery of product, wt. 126 m. This material was identical to that described in Example 10.

Example 17

Ethyl [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-ethoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride (116 mg) in absolute ethanol (30 ml) at 0° for 10 minutes. The reaction mixture was stirred overnight at room temperature and then taken to dryness under reduced pressure. The residue was partitioned between H_2O (10 ml) and ether (20 ml). To this mixture, 0.28 ml of 1M NaOH solution was added. After a few minutes, the layers were separated. The ethereal layer was dried (Na_2SO_4) and then concentrated to give 100 mg of product. Chromatography on silica gel (1:1 Hexane:ethyl acetate, R_f = 0.26) afforded 80 mng of pure product. The mass spectrum showed a molecular ion at 448. 'H MR (300 MHz, $CDCl_3$) δ 1.32 (2 triplets, 6H), 1.60 (br s, 1H), 1.68—2.20 (m, 8H), 2.75 (t, *J*=8Hz, 2H), 3.28 (m, 2H), 3.4 (m, 2H), 3.4 (m, 2H), 4.25 (m, 4H), 5.01 (d, *J*=10Hz, 1H), 5.29 (dd, *J*=6Hz, *J*=3Hz, 1H), 7.28 (m, 5H). Anhydrous hydrogen chloride was bubbled through a solution of the purified diester in ether (30 ml) at 0°. Excess HCl was removed and the title product was collected by filtration, wt. 84 mg; m.p. 68—70°; $[\alpha]_D^{25°} = -52.98°$ (EtOH, c = 0.44).

Anal. Calcd. for $C_{23}H_{32}N_2O_5S$-HCl-1/4H_2O: C, 56.43; H, 6.90; N, 5.72
Found: C, 56.47; H, 6.95; N, 5.42.

Example 18

Benzyl [3*R*-(3α,6α,9aβ)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

[3*R*-(3α,6α,9aβ)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (205 mg) was suspended in 2.5 ml of benzyl alcohol and cooled with an ice bath. Thionyl chloride (0.26 ml) was added. After a few minutes, ice bath was removed and the mixture stirred at room temperature under nitrogen overnight. Ether (30 ml) was added and the resulting precipitate collected, wt. 313 mg. This material was suspended in 20 ml of H_2O and treated with 0.878 ml of 1M NaOH solution. After a few minutes, the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were dried (Na_2SO_4) and concentrated to give 193 mg of pure product. Tlc on silica [1:1:1:1 ethyl acetate: n-butanol:water:acetic acid] indicated a single spot at R_f = 0.74. Mass spectrum showed a molecular ion at 320 m/e. 'H NMR (200 MHz, $CDCl_3$)δ 1.40—2.02 (m, 6H), 1.68 (br s, —NH_2), 3.15 (m, 2H), 3.47 (d, *J*=11Hz, 1H), 4.92 (d, *J*=8Hz, 1H), 5.15 (s, 2H), 5.28 (dd, *J*=7Hz, *J*=3Hz, 1H), 7.32 (s, 5H).

Example 19

Benzyl [3*R*-[3α,6α(*S***R**),9aβ]]-6-[(1-*tert.* butoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

To a solution of Benzyl [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (249 mg) and *t*-butyl 2-oxo-4-phenylbutyrate (910 mg) in absolute ethanol (12 ml), powdered 3A molecular sieves (2.5 g) and 0.045 ml of acetic acid were added. To this mixture, a solution of sodium cyanoborohydride (146 mg) in 2.5 ml of ethanol was added slowly (syringe pump). When reaction was completed, the mixture was filtered and the filtrate concentrated. The residue was partitioned between water and CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to afford an oil, wt. 1.1 g. Chromatography on silice [3:1 hexane:ethyl acetate] permitted the isolation of the diastereomers: *R** diastereomer, 101 mg; exact mass measurement, obs. 538.2470; calcd., 538.2500; 'H NMR (200 MHz, $CDCl_3$) 1.47 (s, 9H), 1.52—2.14 (m, 8H), 2.76 (t, *J*=8Hz, 2H), 3.20 (m, 4H), 4.86 (d, *J*=9Hz, 1H), 5.21 (q, 2H), 5.40 (dd, *J*=6Hz, *J*=3Hz, 1H), 7.26 (m, 5H), 7.39 (s, 5H). *S** diastereomer, 120 mg; exact mass measurement, obs. 538.2465; calcd. 538.2500; 'H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.55—2.16 (m, 8H), 2.32 (br s, N—H), 2.73 (t, *J*=8Hz, 2H), 3.25 (m, 4H), 4.97 (d, *J*=10Hz, 1H), 5.22 (q, 2H), 5.34 (dd, *J*=7Hz, *J*=2.5Hz, 1H), 7.26 (m, 5H), 7.39 (m, 5H).

Example 20

B nzyl [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carboxy-3-phenylpr pyl)amino] ctahydro-5-ox thiaz lo[3,2-*a*]azepine-3-carb xylate hydrochl ride

A s luti n of B nzyl [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-*tert.* butoxycarb nyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (118 mg) in 4N HCl/ethyl acetate was prepared at 0°. The solution was then stirred at room temperature for 3 hours. Concentration and tituration with ether gave the title compound, wt. 114 mg. The mass spectrum showed a molecular ion at 482 m/e for the free base. Tlc on siloica [4:1:1:1 ethyl acetate:n-butanol:water:acetic acid) indicated a single spot, $R_f = 0.57$. $[\alpha]_D^{25°} = -49.9°$ (EtOh, c=0.48); m.p. 111—113°; 'H NMR (200 MHz, CD_3OD) 1.72—2.48 (m, 8H), 2.89 (m, 2H), 3.35 (m, 2H), 4.05 (t, *J*=6Hz, 1H), 4.35 (d, *J*=10.5 Hz, 1H), 5.19 (m, 1H), 5.27 (q, 2H), 5.35 (t, J=4.5 Hz, 1H), 7.38 (m, 10H).

Anal. Calcd. for $C_{26}H_{30}N_2O_5S$—HCl: C, 60.16; H, 6.02; N, 5.40
Found: C, 59.81; H, 6.12; N, 5.15

Example 21

Ethyl [3*R*-[3α,6α,9aβ]]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

[3*R*-(3α,6α,9aβ)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid was dissolved in absolute ethanol which was saturated with anhydrous hydrogen chloride at 0°. The reaction mixture was permitted to stand at room temperature overnight. The mixture was then taken to dryness and the residue neutralized in water. Extraction with CH_2Cl_2 permitted the recovery of the desired product which exhibited spectral properties consistent with its structure.

Example 22

Ethyl [3*R*-[3α,6α(*S***R**),9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate hydrochloride

To a solution of ethyl [3*R*-[3α,6α,9aβ]]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate and *t*-butyl 2-oxo-4-phenylbutyrate in absolute ethanol, powdered 3A molecular sieves and one equivalent of acetic acid were added. To this mixture, a solution of sodium cyanoborohydride in ethanol was slowly added via a syringe pump. When the reaction was completed, the sieves were removed by filtration and the filtrate concentrated. The residue was partitioned between water and CH_2Cl_2. Concentration of the organic phase afforded a mixture of α-ketoester, α-hydroxyester, and the product, ethyl [3*R* - [3α,6α(*S***R**),9aβ]] - 6 - [(1 - *tert.* butoxycarbonyl - 3 - phenylpropyl)amino]octahydro - 5 - oxothiazolo[3,2 - *a*]azepine - 3 - carboxylate. Chromatography on silica permitted the isolation of each diastereomer in high purity. Each diastereomer was deblocked with 4N HCl in ethyl acetate to give the title compounds which exhibited the expected spectral characteristics.

Example 23

[3R-[3α,6α(*S***R**),9aβ]]-6-[(1-Benzyloxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

A solution of [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (200 mg) in 10 ml of H_2O was adjusted to pH 6.3 with 0.5M NaOH solution. The solution was freeze-dried. This residue and benzyl 2-oxo-4-phenylbutyrate (1.165 g) were partly dissolved in absolute ethanol (10 ml). Powdered 3A molecular sieves (2.25 g) were added. To this mixture, a solution of sodium cyanoborohydride (164 mg) in 2 ml of ethanol was slowly added via a syringe pump. When the reaction was completed, the mixture was filtered and the filtrate concentrated. The residue was partitioned between ether (25 ml) and water (25 ml). After separation of the layers, the aqueous phase was adjusted to pH 4.5 with 1M H_3PO_4. This acidified mixture was then repeatedly extracted with chloroform. The organic portion was dried and concentrated to give 239 mg of product. The diastereomers were separated by chromatography on Sephadex LH—20 (MeOH).

The first diastereomer to elute from the column was the (*S**) isomer; wt. 0.103 g. The mass spectrum showed a weak molecular ion at 482 m/e. Tlc on silica [1:1:1:1 Ethyl acetate:n-butanol:water:acetic acid) indicated a single spot, $R_f = 0.85$. 'H NMR (200 MHz, CD_3OD) δ 1.52—2.24 (m, 8H), 2.65 (m, 2H), 3.06—3.37 (m, 2H), 3.69 (m, 2H), 4.92 (m, 1H), 5.09 (m, 1H), 5.26 (q, 2H), 7.22 (m, 5H), 7.45 (m, 5H).

The second diastereomer to elute from the column was the (*R**) isomer, wt. 66 mg. The mass spectrum showed a (M—1) ion at 481. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single spot, $R_f = 0.86$. 'H NMR (200 MHz, CD_3OD) δ 1.50—2.14 (m, 8H), 2.66 (m, 2H), 3.03—3.30 (m, 3H), 3.43 (t, *J*=7Hz, 1H), 4.78 (d, *J*=9Hz, 1H), 5.09 (m, 1H), 5.20 (q, 2H), 7.22 (m, 5H), 7.42 (m, 5H).

Example 24

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Benzyloxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-benzyloxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (85 mg) in ethyl acetate (10 ml). Upon removal of excess HCl, the precipitate was collect d, wt. 93.7 mg $[\alpha]_D^{25°} = -44.1°$ (EtOH, c=0.3).

Anal. Calcd. for $C_{26}H_{30}N_2O_5S$—HCl: C, 60.16; H, 6.02; N, 5.40; S, 6.18; Cl, 6.83
F und: C, 59.78; H, 6.06; N, 5.25; S, 6.19; Cl, 6.36

Example 25

[3R-[3α,6α(*S*R**),9aβ]]-6-[(1-Methoxycarbonyl-3-phenylpr pyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carb xylic acid

To a solution of (3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (252 mg) and methyl 2- xo-4-phenylbutyrate (1.05 g) in methanol (20 ml), powdered 3A m lecular sieves (2.8 g) were added. To this mixtur , a soluti n of sodium cyanob rohydride (205 mg) in 2 ml of m thanol was slowly added via a syringe pump. When the reaction was completed, the mixture was filtered and the filtrate taken to dryness. The residue was partitioned between ether (30 ml) and water (30 ml). The layers were separated and the aqueous layer acidified with 1M H_3PO_4 to pH 3.5. The acidified layer was then extracted repeatedly with chloroform. The chloroform extracts are dried and concentrated to yield 370 mg of the diastereomeric mixture. Separation of diastereomers was achieved by chromatography on Sephadex LH—20 (MeOH).

The first diastereomer to elute from the column was the (*S**) isomer; wt. 0.180 g. The mass spectrum showed a molecular ion at 478 m/e for the monosilylated species. 'H NMR (200 MHz, CD_3OD) δ 1.74—2.28 (m, 8H), 2.77 (t, *J*=7Hz, 2H), 3.26 (m, 2H), 3.70 (t, *J*=6Hz, 1H), 3.77 (s, 3H), 3.84 (m, 1H), 5.13 (m, 2H), 7.28 (m, 5H).

The second diastereomer was the (*R** isomer; wt. 0.101 g. The mass spectrum showed a molecular ion at 406 m/e. 'H NMR (200 MHz, CD_3OD) δ 1.64—2.20 (m, 8H), 2.74 (t, *J*=7Hz, 2H), 3.27 (m, 2H), 3.46 (m, 2H), 3.74 (s, 3H), 5.06 (d, *J*=11Hz, 1H), 5.13 (dd, *J*=7Hz, *J*=3Hz, 1H), 7.26 (m, 5H).

Example 26

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of [3*R* - [3α,6α(*S**),9aβ]] - 6 - [(1 - methoxycarbonyl - 3 - phenylpropyl)amino]octahydro - 5 - oxothiazolo[3,2 - *a*]azepine - 3 - carboxylic acid (0.180 g) in ethyl acetate (20 ml at 0°. Upon removal of excess HCl, the precipitate was collected, wt. 0.188 g $[\alpha]_D^{25°} = -39.5°$ (MeOH, c=1.6).

Anal. Calcd. for $C_{20}H_{26}N_2O_5S$—HCl: C, 54.23; H, 6.14; N, 6.32; S, 7.24; Cl, 8.00
Found: C, 54.14; H, 6.10; N, 6.01; S, 7.17; Cl, 7.93

Example 27

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-methoxycarbonyl-3-phenylpropyl)amino]octahydro-5-oxo-thiazolo[3,2-*a*]azepine-3-carboxylic acid (0.1 g) in ethyl acetate (10 ml) at 0°. Upon removal of excess HCl, the precipitate was collected, wt. 0.105 g $[\alpha]_D^{25°} = 74.1°$ (MeOH, c=0.7).

Anal. Calcd. for $C_{20}H_{26}N_2O_5S$—HCl—H_2O: C, 52.11; H, 6.34; N, 6.08; S, 6.96; Cl, 7.69
Found: C, 52.14; H, 5.98; N, 5.68; S, 6.95; Cl, 7.87

Example 28

[3*R*-[3α,6α(*S*R**),9aβ]]-6-[(1-Ethoxycarbonyl-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

To a solution of [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (0.348 g) and ethyl 5-methyl-2-oxo-hexanoate (1.30 g) in absolute ethanol (15 ml), powdered 3A molecular sieves (3.9 g) were added. To this mixture, a solution of sodium cyanoborohydride (0.285 g) in ethanol (2 ml) was slowly added. When the reaction was completed, the mixture was filtered and the filtrate concentrated to dryness. The residue was partitioned between water (35 ml) and ether (35 ml) and the layers were separated. The aqueous layer was acidified with 1M H_3PO_4 to pH 4.5 and then extracted repeatedly with chloroform. The chloroform layers were dried and then concentrated to yield product, wt. 0.538 g. Separation of the (*S,R**) diastereomers was achieved by chromatography on Sephadex LH—20 (MeOH).

The first diastereomer off the column was the (*S**) isomer: wt. 0.219 g; extract mass measurement, obs. 386.1855, calcd. 386.1874. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single spot, R_f = 0.83. 'H NMR (200 MHz), CD_3OD) δ 0.92 (dd, *J*=7Hz, *J*=2.5Hz, 6H), 1.30 (t, *J*=7Hz, 3H), 1.32 (m, 2H), 1.57 (m, 1H), 1.70—2.26 (m, 8H), 3.24 (m, 2H), 3.68 (t, *J*=6.5Hz, 1H), 3.86 (d, *J*=10Hz, 1H), 4.26 (m, 2H), 5.08 (m, 2H).

The second diastereomer to elute from the column was the (*R**) isomer: wt. 0.210 g; exact mass measurement, obs. 386.1847, calcd. 386.1874. 'H NMR (200 MHz), CD_3OD) δ 0.91 (d, *J*=7Hz, 6H), 1.20 (m, 2H), 1.28 (t, *J*=8Hz, 3H) 1.54 (m, 1H), 1.64—2.20 (m, 8H), 3.23 (m, 2H), 3.49 (m, 2H), 4.21 (m, 2H), 5.13 (m, 2H).

Example 29

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Ethoxycarbonyl-4-methylpentyl)amino]octahydr -5-oxothiazolo[3,2-*a*]az pine-3-carboxylic acid hydrochl rid

Anhydrous hydr gen chloride was bubbled through a s lution of [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-

ethoxycarbonyl-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (114 mg) in ethyl acetate (10 ml) at 0°. Up n removal of excess HCl, the precipitate was collected, wt. 0.120 g $[\alpha]_D^{25°}$ = 54.7° (MeOH, c=0.5).

Anal. Calcd. for $C_{18}H_{30}N_2O_5S$—HCl—0.5H_2O: C, 50.05; H, 7.47; N, 6.49; S, 7.42; Cl, 8.21
Found: C, 49.74; H, 7.36; N, 6.31; S, 7.39; Cl, 8.39

Example 30

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Carboxy-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Ethoxycarbonyl-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (105 mg) was dissolved in methanol (1.5 ml) and treated with 1.4 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. The appropriate fraction was concentrated and dried *in vacuo* to yield a white solid, wt. 97 mg; $[\alpha]_D^{25°}$ = −103.9° (0.1M NaOH, c=0.7). The mass spectrum showed a molecular ion at 502 m/e for the disilylated species. 'H NMR (200 MHz, CD_3OD) δ 0.94 (dd, *J*=7Hz, *J*=2.5Hz, 6H), 1.41 (m, 2H), 1.59 (m, 1H), 1.76—2.36 (m, 8H), 3.30 (m, 2H), 3.60 (t, *J*=6Hz, 1H), 4.20 (d, *J*=8Hz, 1H), 5.20 (m, 2H).

Anal. Calcd. for $C_{16}H_{26}N_2O_5S$—1/4H_2O: C, 52.95; H, 7.36; N, 7.72; S, 8.83
Found: C, 52.86; H, 7.44; N, 7.51; S, 8.64

Example 31

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Carboxy-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Ethoxycarbonyl-4-methylpentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (110 mg) was dissolved in methanol (1.5 ml) and treated with 1.43 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. The appropriate fraction was concentrated and dried to give 96 mg of product. $[\alpha]_D^{25°}$ = −67.8° (0.1M NaOH), c=0.4). The mass spectrum showed a molecular ion at 502 m/e for the disilylated species. 'H NMR (200 MHz, CD_3OD) δ 0.92 (d, *J*=6Hz, 6H), 1.37 (m, 2H), 1.60 (m, 1H), 1.78—2.28 (m, 8H), 3.32 (m, 2H), 3.72 (t, *J*=6Hz, 1H), 4.13 (d, *J*=9Hz, 1H), 5.16 (d, *J*=9Hz, 1H), 5.26 (dd, *J*=6Hz, *J*=3Hz, 1H).

Anal. Calcd. for $C_{16}H_{26}N_2O_5S$—1/4H_2O: C, 52.95; H, 7.36; N, 7.72; S, 8.83
Found: C, 53.00; H, 7.30; N, 7.81; S, 8.53

Example 32

[3*R*-[3α,6α(*S***R**),9aβ]]-6-[[1-Carboxy-3-(4-chlorophenyl)propyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

[3*R*-(3α,6α,9aβ)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (100 mg) and 4-(4-chlorophenyl)-2-oxo-butyric acid (0.692 g) were suspended in 2 ml of water and adjusted to pH 6.1 with 1M NaOH. Sodium cyanoborohydride (82 mg) in 2 ml of water was slowly added via a syringe pump. When reaction was completed, the mixture was absorbed on strong acid ion-exchange resin and eluted with MeOH:H_2O (1:1), H_2O, and then with 3% pyridine in water. The appropriate fractions were concentrated and dried to yield the product, wt. 142 mg. The material was purified by chromatography on Sephadex LH—20 (MeOH) to afford 122 mg of the diastereomeric mixture. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated two spots, R_f = 0.76 and R_f = 0.72 for the two diastereomers. The mass spectrum showed a molecular ion at 453 for the disilylated species minus-COOTMS. 'H NMR (200 MHz, d_6-DMSO) δ 1.40—2.26 (8H), 2.63 (m, 2H), 3.19 (m, 2H), 3.48 (m, 1H), 3.80 (m, 1H), 5.04 (m, 1H), 5.14 (m, 1H), 7.31 (m, 4H).

Example 33

[3*R*-[3α,6α(*S***R**),9aβ]]-6-[[1-(Ethoxycarbonyl)-3-(methylthio)propyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

To a solution of [3*R*-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (0.147 g) and ethyl 4-(methylthio)-2-oxobutyrate (0.564 g) in absolute ethanol (10 ml), powdered 3A molecular sieves (1.7 g) were added. To this mixture, a solution of sodium cyanoborohydride (0.121 g) in ethanol (2 ml) was slowly added via a syringe pump. When the reacton was completed, the mixture was filtered and the filtrate concentrated. The residue was partitioned between water (20 ml) and ether (20 ml) and the layers separated. The aqueous layer was acidified with 1M H_3PO_4 to pH 4.3 and then repeatedly extracted with chloroform. The chloroform layers were dried and then concentrated to give impure product, wt. 0.249 g. Separation of diast re mers was achieved n a Sephadex LH—20 column (MeOH).

The first diastereomer eluted from the column was the (*S**) isomer: wt. 0.067 g. Tlc n silica [3:1:1:1 thyl acetate:n-butanol:wat r:acetic acid] indicated a single spot, R_f = 0.70. 'H NMR (200 MHz, $CDCl_3$) δ

1.29 (t, J=7Hz, 3H), 1.59—2.18 (m, 8H), 2.10 (s, 3H), 2.63 (t, J=7Hz, 2H), 3.18 (m, 1H), 3.37 (m, 1H), 3.50 (t, J=5.5Hz, 2H), 4.22 (m, 2H), 4.82 (br s, 2H, exchangeable), 4.98 (d, J=6Hz, 1H), 5.22 (dd, J=6Hz, J=2Hz, 1H).

The second diastereomer to elute from the column was the (R^*) isomer: wt. 0.065 g. Tlc on silica also indicated a single spot R_f = 0.71. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J=7.5Hz, 3H), 1.54—2.16 (m, 8H), 2.12 (s, 3H), 2.66 (m, 2H), 3.08—3.56 (m, 4H), 4.10 (br S, 2H, exchangeable), 4.20 (m, 2H), 4.92 (m, 1H), 5.29 (d, J=5Hz, 1H).

Example 34

[3R-[3α,6α(S^*,9aβ]]-6-[[1-Carboxy-3-(methylthio)propyl]amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid

[3R-[3α,6α(S^*,9aβ]]-6-[[1-Ethoxycarbonyl-3-(methylthio)propyl]amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid (60 mg) was dissolved in methanol (0.8 ml) and treated with 0.80 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. Concentration of the appropriate fractions yielded the title compound, wt. 56 mg; $[\alpha]_D^{25°} = -94.1°$ (0.1M NaOH, c=0.37). The mass spectrum showed a molecular ion at 506 m/e for the disilylated species. ^{1}H NMR (200 MHz, CD_3OD) δ 1.74—2.32 (m, 8H), 2.12 (s, 3H), 2.70 (t, J=8Hz, 2H), 3.30 (m, 2H), 3.70 (t, J=6Hz, 1H), 4.24 (d, J=10Hz, 1H), 5.18 (m, 2H). HPLC analysis (reverse phase) showed a single peak.

Anal. Calcd. for $C_{14}H_{22}N_2O_5S_2$:	C, 46.39;	H, 6.12;	N, 7.73
Found:	C, 46.81;	H, 6.26;	N, 7.87

Example 35

[3R-[3α,6α(R^*,9aβ]]-6-[[1-Carboxy-3-(methylthio)propyl]amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid

[3R-[3α,6α(R^*),9aβ]]-6-[[1-Ethoxycarbonyl-3-(methylthio)propyl]amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid (64 mg) was dissolved in methanol (0.8 ml) and treated with 0.8 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. The appropriate fraction was concentrated and dried to give the product, wt. 42 mg; $[\alpha]_D^{25°} = -66.4°$ (0.1N NaOH, c=0.26). The mass spectrum showed a (M+1) ion at 507 m/e for the disilylated species. HPLC analysis indicated a single component. ^{1}H NMR (200 MHz, CD_3OD) δ 1.72—2.30 (m, 8H), 2.12 (s, 3H), 2.68 (t, J=6Hz, 2H), 3.30 (m, 2H), 3.84 (t, J=7Hz, 1H), 4.15 (d, J=9Hz, 1H), 5.16 (d, J=8Hz, 1H), 5.24 (dd, J=6Hz, J=3Hz, 1H).

Anal. Calcd. for $C_{14}H_{22}N_2O_5S_2$:	C, 46.39;	H, 6.12;	N, 7.73
Found:	C, 46.22;	H, 6.09;	N, 7.67

Example 36

[3R-[3α,6α(S^*R^*),9aβ]]-6-[[1-(Benzyloxycarbonyl)-5-phthalimidopentyl]amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid

A solution of [3R-(3α,6α,9aβ)]-6-aminooctahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid (159 mg) in 10 ml of water was adjusted to pH 6.65 with dilute NaOH solution. The solution was freeze-dried. This residue and benzyl 2-oxo-6-phthalimidohexanoate [1.26 g, prepared by alkylation of benzyl 1,3-dithiane-2-carboxylate with 4-phthalimidobutyl bromide and subsequent oxidative conversion to the ketone with N-bromosuccinimide] were partly dissolved in 30 ml of absolute ethanol. Powdered 3A molecular sieves (1.7 g) were added. To this mixture, a solution of sodium cyanoborohydride (130 mg) in 3 ml of ethanol was added slowly via a syringe pump. When the reaction had proceeded to completion, the mixture was filtered and the filtrate concentrated. The residue was partitioned between water (50 ml) and ether (25 ml). The layers were separated and the aqueous layer was absorbed on strong acid ion-exchange resin. Elution with water and then 4% pyridine in water permitted the recovery of the product as a mixture of diastereomers, wt. 371 mg. Diastereomers were separated by chromatography on Sephadex LH—20 (MeOH).

The first diastereomer to elute from the column was the (S^*) isomer, wt. 135 mg. The mass spectrum showed a molecular ion at 579 m/e. HPLC analysis (reverse phase) indicated a single diastereomer; ^{1}H NMR (60 MHz, CD_3OD) δ 1.18—2.48 (br m, 12H), 3.18 (br s, 2H), 3.62 (br m, 4H), 5.05 (br s, 2H), 5.21 (s, 2H) 7.35 (s, 5H), 7.78 (s, 4H).

The second diastereomer to come off the column was the (R^*) isomer, wt. 78 mg. HPLC analysis (reverse phase) indicated a single diastereomer. The mass spectrum showed a molecular ion at 579 m/e. ^{1}H NMR (60 MHz, CD_3OD) δ 1.23—2.18 (m, 12H), 3.08—3.85 (m, 6H), 4.93 (m, 2H), 5.12 (s, 2H), 7.30 (s, 5H), 7.78 (s, 4H).

Example 37

[3R-[3α,6α(S^*),9aβ]]-6-[(1-Carboxy-5-aminopentyl)amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid

The reductive alkylation product, [3R-[3α,6α(S),9aβ]]-6-[[1-(benzyloxycarbonyl)-5-phthalimidopentyl]-amino]octahydro-5-oxothiazolo[3,2-a]azepine-3-carboxylic acid (135 mg), in 10 ml of methanol was hydrogenated in the presence of glacial acetic acid (0.012 ml) at 40 psi over 10% palladium on carbon (140

mg). When the deblocking was completed, the catalyst was r moved by filtration and the filtrate c ncentrated. The product, [3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carboxy-5-phthalimidopentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (84 mg), had the expected spectral properties. A solution of this material in 0.75 ml of methanol was treated with hydrazine hydrat (0.15 ml) and then heated at reflux overnight. The precipitated phthalhydrazide was collected and the filtrate taken to dryness. The residue was absorbed on strong acid ion-exchange resin. Elution with water and then 4% pyridine in water afforded a product (43 mg) which was chromatographed on Sephadex LH—20 (MeOH). The title compound (18 mg) was obtained as a white, hygroscopic solid. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single spot, R_f = 0.40. The mass spectrum (Field Desorption) showed a (M+1) molecular ion at 360 m/e 'H NMR (200 MHz, D_2O) δ 1.46—2.38 (m, 12H), 3.08 (t, *J*=7Hz, 2H), 3.18 (d, *J*=5Hz, 2H), 3.68 (t, *J*=7Hz, 1H), 4.20 (d, *J*=9Hz, 1H), 4.97 (m, 1H), 5.19 (m, 1H).

Example 38

[3*R*-[3α,6α(*R**),9aβ]]-6-[(1-Carboxy-5-aminopentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

The protected diastereomer, [3*R*-[3α,6α(*R**),9aβ]]-6-[[1-(benzyloxycarbonyl)-5-phthalimidopentyl]-amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (78 mg), in methanol (10 ml) was hydrogenated at 40 psi over 10% palladium on carbon (80 mg). When the reaction was completed (occasionally, the reaction mixture required recycling), the catalyst was removed and the filtrate taken to dryness. The product, [3*R*-[3α,6α(*R**),9aβ]]-6-[(1-carboxy-5-phthalimidopentyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (29 mg), had the expected spectral properties. A solution of this material in methanol (1.5 ml) was treated with hydrazine hydrate (0.05 ml) and heated at reflux overnight. The precipitate was collected and the filtrate concentrated under reduced pressure. The residue was dried under vacuum to remova excess hydrazine and then absorbed on strong acid ion-exchange resin. Elution with water and then 4% pyridine in water permitted recovery of product (13 mg). Chromatography on Sephadex LH—20 (MeOH) afforded the desired product (3.4 mg). Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single spot, R_f = 0.24. 'H NMR (200 MHz, D_2O) δ 1.36—2.40 (m, 12H), 3.04 (t, *J*=8Hz, 2H), 3.26 (d, *J*=4Hz, 2H), 3.78 (m, 1H), 4.02 (d, *J*=9Hz, 1H), 4.96 (m, 1H), 5.11 (m, 1H).

Example 39

Methyl [3*R*-(3α,6α,9aα)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

Methyl [3*R*-(3α,6α,9aα)]-6-phthalimidooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (1.25 g) was dissolved in 80 ml of absolute ethanol with gentle heating. Hydrazine hydrate (0.178 ml) was added and the mixture stirred at room temperature for 4 days under nitrogen. The reaction mixture was concentrated and the residue dried under vacuum to remove trace amounts of hydrazine. The residue was treated with 0.5M HCl (85 ml) at 0° for 3 hours. The precipitated phthalhydrazide (495 mg) was collected. The filtrate was neutralized with 1M NaOH to pH 10.0 and extracted with CH_2Cl_2. Concentration afforded the amino ester, 0.8 g. Exact mass measurement: obs., 244.0880; calcd., 244.0881. 'H NMR (200 MHz, $CDCl_3$) 1.58 (br s, 2H, NH_2), 1.66—2.20 (br, m, 6H), 3.11 (1/2ABq, J_{AB} = 13Hz, ΔV_{AB} = 35, J_{AX} = 4Hz, 1H), 3.29 (1/2ABq, J_{AB} = 13Hz, ΔV_{AB} = 35, J_{BX} = 7Hz, 1H), 3.76 (s, 3H), 3.87 (m, 1H, 5.23 (dd, *J*=7Hz, *J*=4Hz, 1H), 5.55 (d, *J*=10Hz, 1H).

Example 40

[3*R*-(3α,6α,9aα]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

Methyl [3*R*-(3α,6α,9aα]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate (0.8 g) was dissolved in 15 ml of methanol and treated with 13.5 ml of 1M NaOH solution. The reaction mixture was stirred overnight at room temperature under nitrogen and then absorbed on strong acid ion-exchange resin. Elution with 3% pyridine in water permitted the recovery of the product, 653 mg. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single component, R_f = 0.65. Exact mass measurement, obs. 230.0727; calcd. 230.0725. 'H NMR (200 MHz, D_2O) δ 1.94—2.62 (m, 6H), 3.19 (1/2ABq, J_{AB} = 12Hz, ΔV_{AB} = 57, J_{AX} = 8Hz, 1H), 3.45 (1/2ABq, J_{AB} = 12Hz, ΔV_{AB} = 57, J_{BX} = 7Hz, 1H), 4.39 (d, *J*=11Hz, 1H), 4.96 (m, 1H), 5.21 (d *J*=9Hz, 1H).

Example 41

Methyl [3*R*-[3α,6α(*S***R**),9aα]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

A solution of methyl [3*R*-(3α,6α,9aα)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate hydrochloride (152 mg) in aqueous methanol (10 ml, 1:1) was adjusted to pH 6.2 with 0.5M NaOH solution. The solution was concentrated and then redissolved in absolute methanol (10 ml). Methyl 2-oxo-4-phenylbutyrate (0.78 g) and powdered 3A molecular sieves (1.5 g) were added. A solution of sodium cyanoborohydride (102 mg) in methanol (3.5 ml) was slowly added via a syringe pump. When the reaction was completed, th sieves were removed by filtration and th filtrate concentrated. The residue was partitioned between CH_2Cl_2 (50 ml) and water (50 ml). The CH_2Cl_2 layer was dried and then concentrated t dryness. The diastereomers wer separat d by silica g l chromatography with 1:1 hexane:ethyl acetate as eluant.

The first diastereomer (R_f = 0.35) eluted from the column was methyl [3*R*-[3α,6α(*R**),9aα]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amin]octahydr -5-oxothiazolo[3,2-*a*]azepine-3-carboxylate, wt. 78 mg. 'H NMR (200 MHz, $CDCl_3$) δ 1.53—2.22 (m, 8H), 2.72 (t, *J*=8Hz, 2H), 3.12 (m, 1H), 3.28 (m, 1H), 3.54 (m, 1H), 3.66 (m, 1H), 3.76 (s, 6H), 5.24 (dd, *J*=7Hz, *J*=3Hz, 1H), 5.70 (d, *J*=10Hz, 1H), 7.28 (m, 5H); exact mass measurement, obs. 420.1685, calcd. 420.1718.

Anal. Calcd. for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66; S, 7.63
Found: C, 60.05; H, 6.93; N, 6.52; S, 7.79

The second diastereomer (R_f = 0.26) to come off the column was methyl [3*R*-[3α,6α(*S**),9aα]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate wt. 120 mg. This isomer was recrystallized from ether-petroleum ether (1:1), m.p. 123.5—24°. 'H NMR (200 MHz, $CDCl_3$) δ 1.60—2.23 (m, 8H), 2.84 (m, 2H), 3.14 (m, 1H), 3.30 (m, 1H), 3.63 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 5.24 (dd, *J*=7Hz, *J*=3Hz, 1H), 5.97 (d, *J*=10Hz, 1H), 7.28 (m, 5H); exact mass measurement, obs. 420.1725, calcd. 420.1718.

Anal. Calcd. for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66; S, 7.63
Found: C, 60.12; H, 6.77; N, 6.46; S, 7.93

Example 42

[3*R*-[3α,6α(*S**),9aα]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

Methyl [3*R*-[3α,6α(*S**),9aα]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo-[3,2-*a*]azepine-3-carboxylate (125 mg) was dissolved in 1 ml of MeOH and 2 ml of 1M NaOH solution (gentle heating was required). After standing overnight at room temperature, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. The appropriate fraction was concentrated and dried to afford a white solid, wt. 99 mg. Recrystallized from water-methanol to give fine white needles, wt. 76 mg; m.p. 191.5—93° (dec); Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single component, R_f = 0.75; I.R. (KBr): 1725 and 1622 cm^{-1}; 'H NMR (200 MHz, d_6-DMSO) δ 1.42—2.24 (m, 8H), 2.76 (m, 2H), 3.03 (dd, *J*=12Hz, *J*=2.5Hz, 1H), 3.38 (m, 3H), 4.99 (d, *J*=5Hz, 1H), 5.94 (d, *J*=9Hz, 1H), 7.26 (m, 5H); $[\alpha]_D^{25°}$ = −57.7° (0.1M NaOH, c=0.39).

Anal. Calcd. for $C_{19}H_{24}N_2O_5S—H_2O$: C, 55.59; H, 6.39; N, 6.83; S, 7.81
Found: C, 55.56; H, 6.45; N, 6.69; S, 7.90

Example 43

[3*R*-[3α,6α(*R**),9aα]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

Methyl [3*R*-[3α,6α(*R**),9aα]] - 6 - [[1 - methoxycarbonyl - 3 - phenylpropyl)amino]octahydro - 5 - oxothiazolo[3,2-*a*]azepine-3-carboxylate (28 mg) was dissolved in 2 ml of methanol and 0.5 ml of 1M NaOH solution. After standing overnight, the reaction mixture was absorbed on strong acid ion-exchange resin and eluted with 3% pyridine in water. Concentration of the appropriate fraction yielded 26 mg of product. Mass spectrum showed a molecular ion at 536 m/e for the disilylated species. Tlc on silica [1:1:1:1 ethyl acetate:n-butanol:water:acetic acid] indicated a single component, R_f = 0.75. 'H NMR (200 MHz, d_6-DMSO) δ 1.58 (m, 2H), 1.94 (m, 6H), 2.67 (t, *J*=8Hz, 2H), 3.04 (dd, *J*=12Hz, *J*=3Hz, 1H), 3.39 (m, 3H), 4.99 (dd, *J*=7Hz, *J*=3Hz, 1H), 5.64 (d, *J*=9Hz, 1H), 7.28 (m, 5H).

Example 44

[3*R*-[3α,6α(*S***R**),9aα]]-6-[[1-(Ethoxycarbonyl)-3-phenyl-propyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid

A solution of [3*R*-[3α,6α,9aα)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid (0.133 g) in 10 ml of water was adjusted to pH 6.7 with dilute NaOH solution. The solution was then freeze-dried. The residue and ethyl 2-oxo-4-phenylbutyrate (0.596 g) were dissolved in 10 ml of absolute ethanol. Powdered 3A molecular sieves (1.5 g) were added. To this mixture, a solution of sodium cyanoborohydride (0.109 g) in 2 ml of ethanol was slowly added via a syringe pump. When the reaction was completed, the mixture was filtered and the filtrate concentrated. The residue was partitioned between water (50 ml) and ether (50 ml). The layers were separated and the aqueous phase was absorbed on strong acid ion-exchange resin. Elution with water and then 3% pyridine in water permitted the isolation of the title compound as a mixture of diastereomers, wt. 200 mg. The mass spectrum was consistent with the structure and HPLC analysis (reverse phase) indicated approximately a 60:40 mixture of diastereomers. 'H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, *J*=7Hz, 3H), 1.52—2.20 (m, 8H), 2.74 (m, 2H), 3.23 (m, 2H), 3.54 (m, 2H), 4.18 (m, 2H), 5.22 (m, 1H), 5.64 and 5.92 (d, 1H) 5.82 (br s, 2H, exchangeable), 7.26 (m, 5H). The diastereomers can be separated by chromatography on a reverse phase column.

Example 45

Ethyl [3*R*-[3α,6α(*S***R**),9aα]]-6-[[1-(eth xycarbonyl)-3-ph nylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

Anhydrous hydrog n chlorid was bubbled through a s luti n of [3*R*-[3α,6α(*S***R**),9aα]]-6-[[1-eth xycarbonyl)-3-phenylpropyl]amin]octahydr -5- xothiazolo[3,2-*a*]azepine-3-carboxylic acid in

absolute ethanol at 0° for 15 minutes. The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was partitioned between water and ether and the neutralized. The ethereal layer was dried and then taken to dryness to afford an oil as a mixture of diastereomer. The diastereomers can be separated by chromatography. Each diastereomer exhibited the characteristic mass spectra and 'HNMR spectra were consistent with their structures.

Example 46

Benzyl [3*R*-[3α,6α,9aα(]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

[3*R*-[3α,6α,9aα)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid was suspended in benzyl alcohol at 0° and treated with thionyl chloride. The reaction mixture was stirred overnight at room temperature and under an inert atmosphere. Ether was added and the precipitate collected. This material was suspended in water and then neutralized with one equivalent of base to afford, upon extraction, the desired compound. Tlc, mass spectrum, and 'HNMR were consistent with its structure.

Example 47

Benzyl [3*R*-[3α,6α(*S***R**),9aα]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate Hydrochloride

To a solution of benzyl [3*R*-[3α,6α,9aα]]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate and *t*-butyl 2-oxo-4-phenylbutyrate in absolute ethanol, powdered 3A molecular sieves and one equivalent of acetic acid were added. To this mixture, a soluton of sodium cyanoborohydride in ethanol was slowly added. When reaction was completed, standard work-up yielded the product, Benzyl [3*R*-[3α,6α(*S***R**), 9aα]] - 6 - [[1 - (*tert.*butoxycarbonyl) - 3 - phenylpropyl]amino]octahydro - 5 - oxothiazolo[3,2-*a*]azepine - 3-carboxylate, as a mixture of diastereomers. Chromatography permitted the separation of the diastereomers and deblocking with 4N HCl in ethyl acetate provided the title compounds. Each diastereomers displayed spectra properties consistent with their structures.

Example 48

Ethyl [3*R*-(3α,6α,9aα)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate

[3*R*-(3α,6α,9aα)]-6-Aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid was dissolved in ethanol at 0° and the solution saturated with anhydrous hydrogen chloride. The reaction mixture was then stirred overnight at room temperature. The mixture was taken to dryness and the residue suspended in water. Neutralization with base and then extraction afforded the title compound.

Example 49

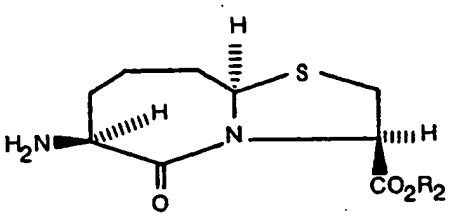
Ethyl [3*R*-[3α,6α(*S***R**),9aα]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate Hydrochloride

To a solution of ethyl [3*R*-[3α,6α,9aα)]-6-aminooctahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate and *t*-butyl 2-oxo-4-phenylbutyrate in absolute ethanol, powdered 3A molecular sieves and one equivalent of acetic acid were added. To this mixture, a solution of sodium cyanoborohydride in ethanol was slowly added. When the reaction was completed, the sieves were removed by filtration and the filtrate concentrated. The residue was partitioned between water and CH_2Cl_2. Concentration of the CH_2Cl_2 portion afforded the product, ethyl [3*R*-[3α,6α(*S***R**),9aα]] - 6 - [[1 - *tert.*butoxycarbonyl) - 3 - phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate, as a mixture of diastereomers along with excess α-ketoester and α-hydroxy ester. Chromatography on silica permitted the isolation of each diastereomer in high purity. Each diastereomer was deblocked with 4N HCl in ethyl acetate to give the title compounds which exhibited their expected spectral properties.

Example 50

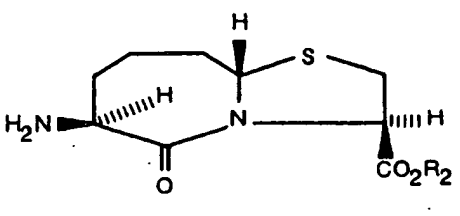
Additional Products of Formula (I)

Additional keto acids and keto esters listed in Table I below as well as those employed in the foregoing examples can be reductively condensed with intermediates



(VIIIa)

and



(VIIIb)

by the methods described hereinabove to yield, after removal of protecting groups, if any, products of

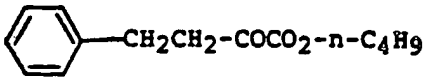
Formula I listed bel w in Table II. In intermediates VIIIa and VIIIb, R_2 can be hydrog n, benzyl, phenyl, methyl, ethyl, n-butyl, and allyl groups. The latter ester groups can be introduced by methods analogous with the benzyl ester synthesis or by methods indicated in footnote 5 to Tabl II. In Table II, the stereochemistry at 9a refers to the hydrogen configuration being R or S at the ring structure in th bicyclic lactam part-structure of Formula (I) compounds.

TABLE I

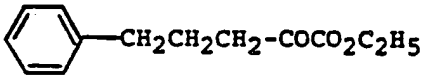
KETO ACIDS AND KETO ESTERS OF THE FORMULA:

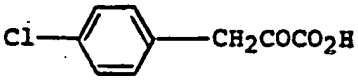
R_1COCO_2R

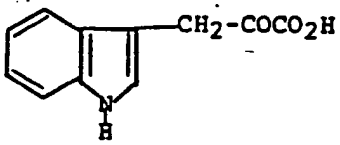
(IX)

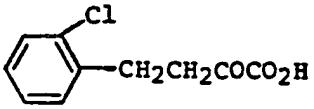
(a) 

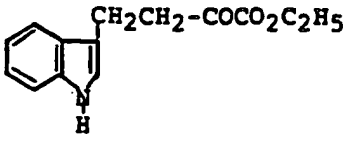
(b) 

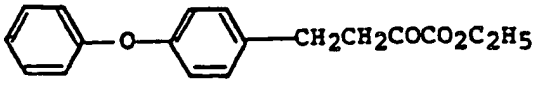
(c) 

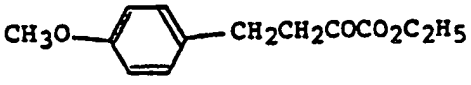
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

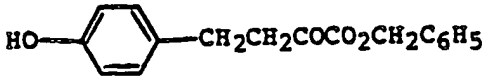
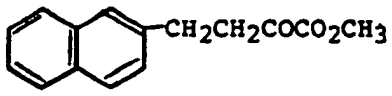
(j) 

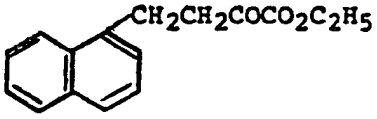
TABLE I (Continued)

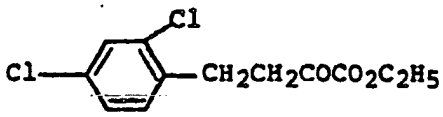
KETO ACIDS AND KETO ESTERS OF THE FORMULA:

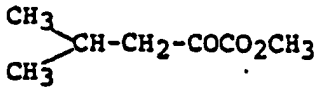
R_1COCO_2R

(IX)

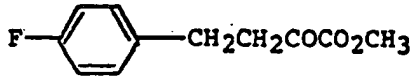
(k) 

(l) 

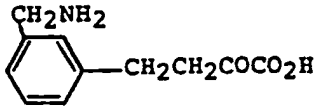
(m) 

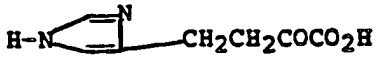
(n) 

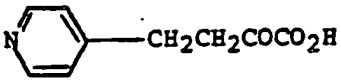
(o) $CH_3CH_2CH_2CH_2-COCO_2C_2H_5$

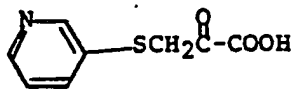
(p) 

(q) $NH_2-(CH_2)_5-COCO_2H$ (1)

(r)  (1)

(s)  (2)

(t) 

(u) 

(v) $HOCH_2CH_2 - COCO_2C_2H_5$ (3)

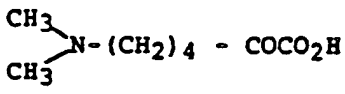
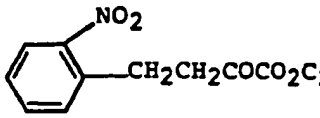
(w) 

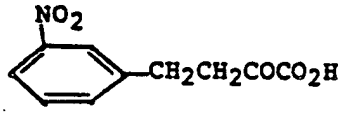
TABLE I (Continued)

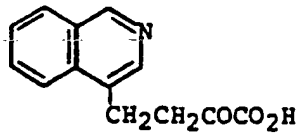
KETO ACIDS AND KETO ESTERS OF THE FORMULA:

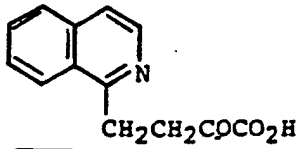
R_1COCO_2R

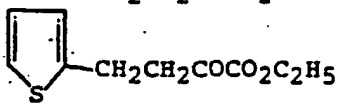
(IX)

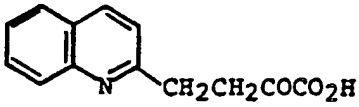
(x)  (4)

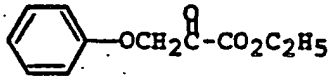
(y)  (4)

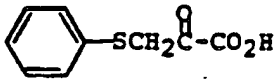
(z) 

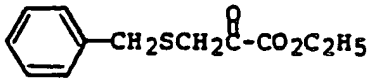
(aa) 

(bb) 

(cc) 

(dd) 

(ee) 

(ff) 

(1) Protected as the N-phthaloyl derivative.

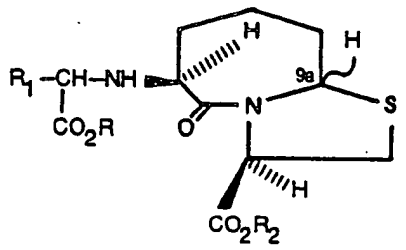
(2) 2-Imidazole NH protected as the N-benzyl derivative.

(3) Protected as the O-benzyl derivative.

(4) Precursor to m-amino derivative by H_2/Pd.

TABLE II

Additional Products of Formula (I):



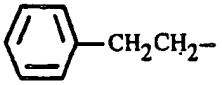
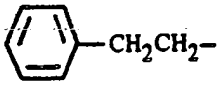
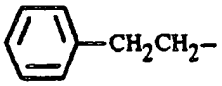
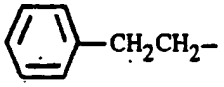
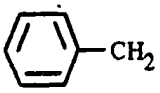
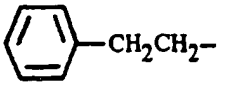
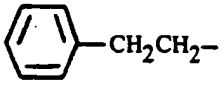
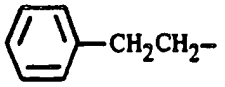
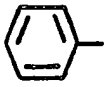
	R	R_1	R_2	(9a) Stereochemistry
(1)	n-C_4H_9–		H–	S
(2)	CH_2 = CH–CH_2–		C_2H_5–	R
(3)	C_2H_5–		C_2H_5–	S
(4)	C_2H_5–		CH_2 = CH–CH_2– (5)	R
(5)			H–	S
(6)	CH_3–		n-C_4H_9– (5)	S
(7)	H–			R

TABLE II (Continued)

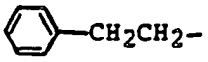
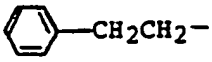
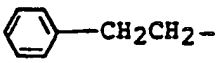
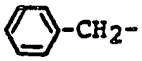
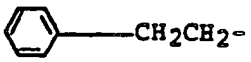
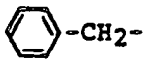
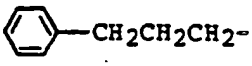
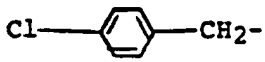
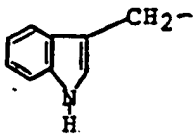
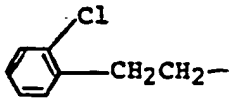
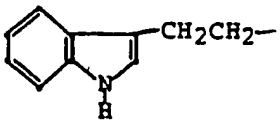
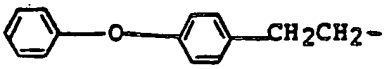
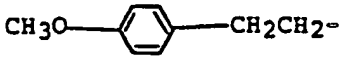
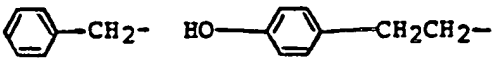
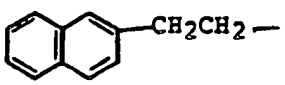
R	R_1	R_2	(9a) Stereochemistry
(8) CH_3-		$n\text{-}C_4H_9$- (5)	R
(9) CH_3-		C_2H_5-	R
(10) CH_3-			S
(11) H-			S
(12) C_2H_5-		H-	R
(13) H-		H-	R
(14) H-		H-	R
(15) H-		H-	R
(16) C_2H_5-		CH_3-	R
(17) C_2H_5-		H-	R
(18) C_2H_5-		$n\text{-}C_4H_9$-	S
(19)		H-	R
(20) CH_3-		C_2H_5-	S

TABLE II (Continued)

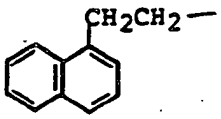
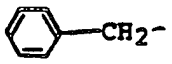
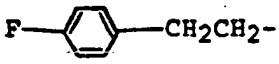
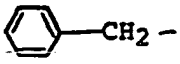
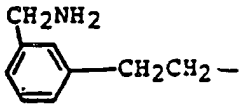
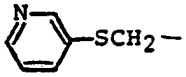
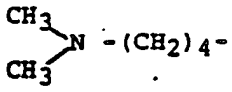
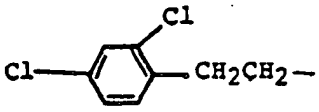
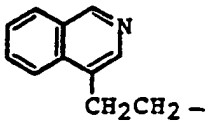
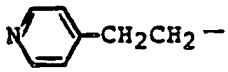
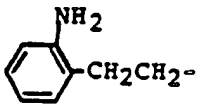
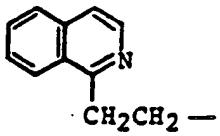
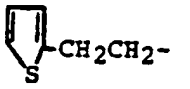
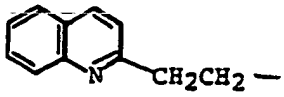
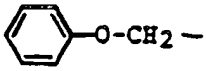
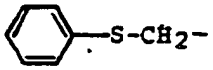
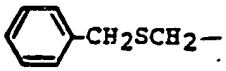
	R	R_1	R_2	(9a) Stereochemistry
(21)	C_2H_5–		 R	
(22)	C_2H_5-	CH_3S-CH_2CH_2-	H–	S
(23)	CH_3–	$(CH_3)_2$-CH-CH_2-	n-C_4H_9–	S
(24)	C_2H_5-	$CH_3CH_2CH_2CH_2$–	C_2H_5–	R
(25)	CH_3-		 R	
(26)	H–	$NH_2(CH_2)_5$-	H –	S
(27)	H –		H –	S
(28)	H –		H –	S
(29)	H –		H –	R
(30)	C_2H_5 –	$HOCH_2CH_2$-	– C_2H_5 –	R
(31)	H –		H –	S
(32)	C_2H_5 –		CH_3 –	S
(33)	H –		H –	S
(34)	H –		H –	R

TABLE II (Continued)

	R	R_1	R_2	(9a) Stereochemistry
(35)	C_2H_5 —		H —	S
(36)	C_2H_5 —		C_2H_5 —	S
(37)	C_2H_5 —		CH_2=CH-CH_2 —	S
(38)	H —		H —	R
(39)	C_2H_5 —		H —	S
(40)	H —		H —	R
(41)	C_2H_5 —		H —	R

(5) The required R_2 ester can be prepared by first protecting (VIII) as its t-BOC derivative and then reacting it with DCC and the desired alcohol or phenol in the presence of 4-dimethylamino pyridine. In some examples, the R_2 ester can also be introduced by reaction of protected (VIII) with cesium carbonate and the appropriate alkyl halide in DMF.

Example 51

Compressed Tablet containing 5 mg of active ingredient

	Per tablet, mg
[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]-octahydro-5-oxothiazol [3,2-*a*]az pine-3-carb xylic acid	5
Calcium phosphate dibasic	245
Ethyl cellulose (as 5% solution in ethanol)	5
Unmixed granulation	255
Add:	
Starch, corn	14
Magnesium stearate	1
	270

Example 52

Dry filled capsule containing 5 mg of active ingredient of Example 51.

	Per capsule, mg
Lactose	5
Magnesium stearate	273
Mixed powders	2
	280

Mix the active ingredient above, lactose, and magnesium stearate and reduce to a No. 60 mesh powder. Encapsulate, filling 285 mg in each No. 2 capsule.

Example 53

Compressed Tablet containing 5 mg of active ingredient

	Per tablet, mg
[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid	5
Calcium phosphate dibasic	245
Ethyl cellulose (as 5% solution in ethanol)	5
Unmixed granulation	255
Add:	
Starch, corn	14
Magnesium stearate	1
	270

Example 54

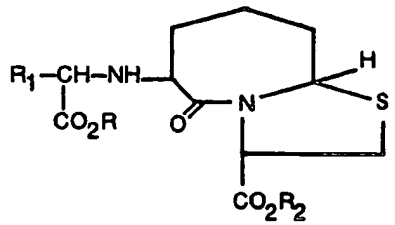
Dry filled capsule containing 5 mg of active ingredient of Example 53.

	Per capsule, mg
Lactose	5
Magnesium stearate	273
Mix d powders	2
	280

Mix the active ingredient above, lactose, and magnesium stearate and reduce t a No. 60 m sh powder. Encapsulate, filling 285 mg in each No. 2 capsule.

Claims

1. A compound of the formula (I)



(I)

wherein:

R and R_2 are independently hydrogen, C_{1-6} alkyl, phenyl, naphthyl, biphenyl and corresponding aralkyls having 1—6 carbon atoms in the alkyl moiety,

R_1 is hydrogen; alkyl having 1 to 12 carbon atoms, cycloalkyl having up to 12 carbon atoms, alkenyl having up to 12 carbon atoms and alkynyl having up to 12 carbon atoms; C_{1-6} alkyl substituted by halo, hydroxy, carboxy, C_{1-6} alkylthio, C_{1-6} alkoxy, C_{1-6}alkoxy carbonyl, phenyl-, naphthyl- or biphenyl-C_{1-6}-alkoxy carbonyl, amino, C_{1-6} alkylamino, di(C_{1-6}-alkyl)amino, or C_{1-6} alkanoylamino or aroylamino; a residue having the formula $R^A(CH_2)_n$—Q—$(CH_2)_m$ wherein n is 0—2, m is 1—3, R^A is phenyl, naphthyl, biphenyl, indolyl, thienyl, imidazolyl, furyl, benzimidazolyl, pyridyl, quinolinyl, isochinolinyl, or benzothienyl whereby the aryl and heteroaryl moieties are optionally substituted by amino, di(C_{1-6}-alkyl)amino, C_{1-6} alkylamino, hydroxy, hydroxy-C_{1-6}-alkyl, amino-C_{1-6}-alkyl, trihalo-C_{1-6}-alkyl, cyano, nitro, sulfonamido, aroyl, C_{1-6} alkyl, 1 or 2 halogens and C_{1-6} alkoxy, and Q is O, S, N—R^B, —$CONR^C$—, —NR^CCO— or —CH=CH— wherein R^B is hydrogen, C_{1-6} alkyl, phenyl, naphthyl, biphenyl, aralkyl having 1 to 6 carbon atoms in the alkyl and "ar" defining phenyl, naphthyl or biphenyl, C_{1-6} alkanoyl or aroyl; and R^C is hydrogen or C_{1-6} alkyl; phenyl, naphthyl or biphenyl wherein the aryls can be substituted by C_{1-6} alkyl, amino-C_{1-6}-alkyl, C_{1-6} alkoxy, phenyl-, naphthyl- or biphenyloxy, aroyl, hydroxy, 1 or 2 halogens; aralkyl or heteroaralkyl wherein the alkyl portion contains 1 to 6 carbon atoms and the aryl and heteroaryl moiety is defined as for R^A whereby the C_{1-6} alkyl groups can be substituted by amino C_{1-6} alkanoylamino, aroylamino or hydroxyl and the aryl and heteroaryl groups can be substituted by 1 or 2 halogens, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, phenyl-, naphthyl- or biphenyloxy, aroyl, phenyl, naphthyl- or biphenylthio, amino, amino-C_{1-6}-alkyl, C_{1-6} alkanoyl amino, aroylamino, di-C_{1-6}-alkylamino, C_{1-6} alkylamino, hydroxy, hydroxy-C_{1-6}-alkyl, trihalo-C_{1-6}-alkyl, nitro, cyano, or sulfonamido;
and the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 which is a member of the group:

[3*R*-[3α,6α(*S**), 9aα]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid;

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid;

[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-α]azepine-3-carboxylic acid; and

[3*R*-[3β,6α(*S**), 9aβ]]-6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylic acid.

3. A compound of Claim 1 which is a member of the group: n-Butyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[[1-methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate;

Ethyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate;

Ethyl [3*R*-[3α,6α(*S**), 9aα]]-6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate;

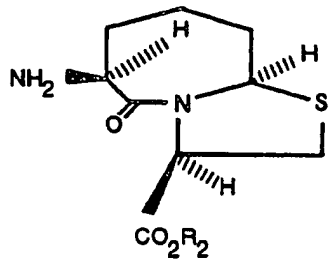
Benzyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepine-3-carboxylate;

Phenyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]occtahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate;

n-Butyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl)amino] ctahydro-5-x thiazolo[3,2-*a*]-azepine-3-carboxylate; and,

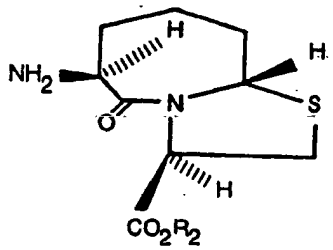
Benzyl [3*R*-[3α,6α(*S**), 9aβ]]-6-[[1-(m thoxycarbonyl)-3-phenylpr pyl]amin] ctahydro-5-oxothiazolo[3,2-*a*]-azepine-3-carboxylate.

4. A compound having the formula:



wherein R_2 is hydrogen, C_{1-6}-alkyl, phenyl, naphthyl, biphenyl and corresponding aralkyls having 1—6 carbon atoms in the alkyl moiety.

5. A compound having the formula



wherein R_2 is hydrogen, C_{1-6}-alkyl, phenyl, naphthyl, biphenyl and corresponding aralkyls having 1—6 carbon atoms in the alkyl moiety.

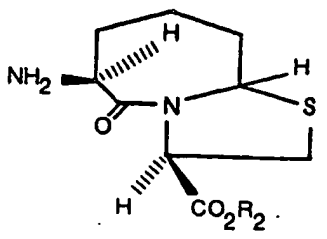
6. A pharmaceutical composition useful in the treatment of hypertension which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 1.

7. The composition of Claim 6 which includes another antihypertensive and/or diuretic compound selected from the group amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetate and cryptenamine tannates, deserpidine, diazoxide, ethacrynic acid, furosemide, guanethidene sulfate, hydralazine hydrochloride, hydrochlorothiazide, hydroflumethiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, (S)-1-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-3-{[4-(2-thienyl)-1H-imidazol-2-yl]phenoxy}-2-propanol, polythiazide, the pivaloyloxyethyl ester of methyldopa, indacrinone and variable ratios of its enantiomers, nifedipine, verapamil, diltiazam, flumethiazide, bendroflumethiazide, atenolol, (+)-4-{3-{[2-(1-hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl}propyl}benzoic acid, bumetanide, prazosin, propanolol, *rauwolfia serpentina,* rescinnamine, reserpine, spironolactone, timolol, trichlormethiazide, benzthiazide, quinethazone, tricrynafan, triamterene, acetazolamide, aminophylline, cyclothiazide and merethoxylline procain, as well as admixtures and combinations thereof.

8. The composition of Claim 6 wherein said pharmaceutically effective compound is a member of the group according to claim 2.

9. The composition of claim 6 wherein said pharmaceutically effective compound is a member of the group according to claim 3.

10. A process for producing a compound of claim 1 which process comprises:
synthesizing a bicyclic lactam having the formula (VIII)



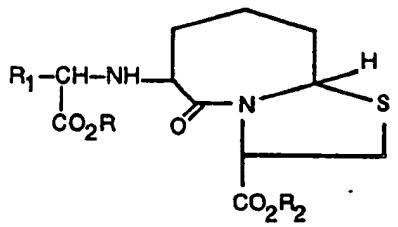
(VIII)

wherein R_2 is as defined ab ve, and subsequently reductively alkylating said lactam with α-ket acids and

esters, followed by rem val of protecting groups, if any, to yield products f F rmula (I) and, if d sired, is lating the biologically more activ diast reomer by chromatography or crystallization and, if further desired, preparing a pharmaceutically acceptable salt therefrom by conventional means.

Patentansprüche

1. Eine Verbindung der Formel (I)



(I)

worin:

R und R_2 sind unabhängig voneinander Wasserstoff, C_{1-6}-Alkyl, Phenyl, Naphthyl, Biphenyl und entsprechende Aralkylreste mit 1—6 Kohlenstoffatomen im Alkylrest;

R_1 ist Wasserstoff; Alkyl mit 1 bis 12 Kohlenstoffatomen, Cycloalkyl mit bis zu 12 Kohlenstoffatomen, Alkenyl mit bis zu 12 Kohlenstoffatomen und Alkinyl mit bis zu 12 Kohlenstoffatomen; C_{1-6}-Alkyl, substituiert durch Halogen, Hydroxy, Carboxy, C_{1-6}-Alkylthio, C_{1-6}-Alkoxy, C_{1-6}-Alkoxycarbonyl, Phenyl-, Naphthyl- oder Biphenyl-C_{1-6}-alkoxycarbonyl, Amino, C_{1-6}-Alkylamino, Di-C_{1-6}-alkyl)-amino oder C_{1-6}-Alkanoylamino oder Aroylamino; ein Rest der Formel $R^A(CH_2)_n$—Q—$(CH_2)_m$, worin n 0—2 ist, m 1—3 ist, R^A Phenyl, Naphthyl, Biphenyl, Indolyl, Thienyl, Imidazolyl, Furyl, Benzimidazolyl, Pyridyl, Chinolinyl, Isochinolinyl oder Benzothienyl bedeutet, wobei die Aryl- und Heteroarylreste gegebenenfalls durch Amino, Di-(C_{1-6}-alkyl)-amino, C_{1-6}-Alkylamino, Hydroxy, Hydroxy-C_{1-6}-alkyl, Amino-C_{1-6}-alkyl, Trihalogen-C_{1-6}-alkyl, Cyano, Nitro, Sulfonamido, Aroyl, C_{1-6}-Alkyl, 1 oder 2 Halogenatome und C_{1-6}-Alkoxy substituiert sind, und Q O, S, N—$R^B{}_1$—$CONR^c$—, —NR^cCO— oder —CH=CH— bedeutet, wobei R^B Wasserstoff, C_{1-6}-Alkyl, Phenyl, Naphthyl, Biphenyl, Aralkyl mit 1 bis 6 Kohlenstoffatomen im Alkyl und mit der Bedeutung "ar" = Phenyl, Naphthyl oder Biphenyl, C_{1-6}-Alkanoyl oder Aroyl bedeutet, und R^C Wasserstoff oder C_{1-6}-Alkyl ist; Phenyl, Naphthyl oder Biphenyl, worin die Arylreste durch C_{1-6}-Alkyl, Amino-, C_{1-6}-alkyl, C_{1-6}-Alkoxy, Phenyl-, Naphthyl- oder Biphenyloxy, Aroyl, Hydroxy, 1 oder 2 Halogenatome substituiert sein können;

Aralkyl oder Heteroaralkyl, worin der Alkylteil 1 bis 6 Kohlenstoffatome enthält und der Aryl- und Heteroarylrest die für R^N definierte Bedeutung besitzt, wobei die C_{1-6}-Alkylreste durch Amino, C_{1-6}-Alkanoylamino, Aroylamino oder Hydroxyl substituiert sein können und die Aryl- oder Heteroarylgruppen durch 1 oder 2 Halogenatome, C_1-Alkyl, Hydroxy, C_{1-6}-Alkoxy, Phenyl-, Naphthyl- oder Biphenyloxy, Aroyl, Phenyl-, Naphthyl- oder Biphenylthio, Amino, Amino-C_{1-6}-alkyl, C_{1-6}-Alkanoylamino, Aroylamino, Di-C_{1-6}-alkylamino, C_{1-6}-Alkylamino, Hydroxy, Hydroxy-$_{1-6}$-alkyl, Trihalogen-C_{1-6}-alkyl, alkyl, Nitro, Cyano oder Sulfonamido substituiert sein können;

und die pharmazeutisch verträglichen Salze davon.

2. Eine Verbindung nach Anspruch 1 aus folgender Gruppe:

[3*R*-[3α,6α(*S**),9aα]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepin-3-carbonsäure;

[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-Carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]azepin-3-carbonsäure;

[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(Äthoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepin-3-carbonsäure; und

[3*R*-[3α,6α(*S**),9aα]]-6-[[1-(Äthoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepin-3-carbonsäure.

3. Eine Verbindung nach Anspruch 1 aus folgender Gruppe:

n-Butyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepin-3-carboxylat;

Äthyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(äthoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepin-3-carboxylat;

Äthyl-[3*R*-[3α,6α(*S**),9aα]]-6-[[1-(äthoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]azepin-3-carboxylat;

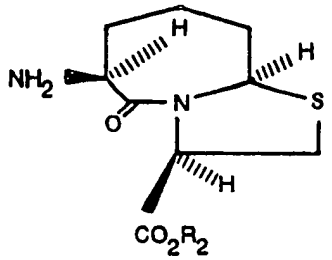
Benzyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carboxy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*3a*]azepin-3-carb xylat;

Phenyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[(1-carb xy-3-phenylpropyl)amino]octahydro-5-oxothiazolo[3,2-*a*]-azepin-3-carboxylat;

n-Butyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepin-3-carboxylat; und

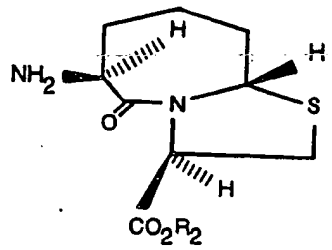
Benzyl-[3*R*-[3α,6α(*S**),9aβ]]-6-[[1-(methoxycarbonyl)-3-phenylpropyl]amino]octahydro-5-oxothiazolo[3,2-*a*]-azepin-3-carboxylat.

4. Eine Verbindung der Formel



in der R_2 Wasserstoff, C_{1-6}-Alkyl, Phenyl, Naphthyl, Biphenyl und entsprechende Aralkylreste mit 1—6 Kohlenstoffatomen im Alkylrest bedeutet.

5. Eine Verbindung der Formel



in der R_2 Wasserstoff, C_{6-6}-Alkyl, Phenyl, Naphthyl, Biphenyl und entsprechende Aralkylreste mit 1—6 Kohlenstoffatomen im Alkylrest bedeutet.

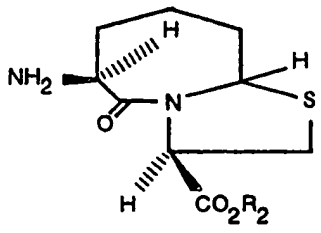
6. Eine pharmazeutische Zusammensetzung zur Behandlung von Hochdruck, die einen pharmazeutisch verträglichen Träger und eine pharmazeutisch wirksame Menge einer Verbindung nach Anspruch 1 enthält.

7. Zusammensetzung nach Anspruch 6, die eine weitere antihypertensive und/oder diuretische Verbindung aus der Gruppe Amilorid, Atenolol, Bendroflumethiazid, Chlorothalidon, Chlorothiazid, Clonidin, Cryptenamin-acetat und Cryptenamin-tannate, Deserpidin, Diazoxid, Ethacrynsäure, Furosemid, Gaunethiden-sulfat, Hydralazin-hydrochlorid, Hydrochlorothiazid, Hydroflumethiazid, Metolazon, Metoprolol-tartrate, Methyclothiazid, Methyldopa, Methyldopat-hydrochlorid, Minoxidil, (S)-1-{[2-(3,4-Dimethoxyphenyl)-äthyl]-amino}-3-{[4-2-thienyl)-1H-imidazol-2-yl]-phenoxy}-2-propanol, Polythiazid, Pivaloyloxyäthylester von Methyldopa, Indacrinon und verschiedene Verhältnisse seiner Enantiomeren, Nifepidin, Verapamil, Diltiazam, Flumethiazid, Bendroflumethiazid, Atenolol, (+)-4-{3-{[2-(1-hydroxycyclohexyl)-äthyl]-4-oxo-2-thiazolidinyl}-propyl}-benzoesäure, Bumetanid, Prazosin, Propranolol, Rauwolfia serpentina, Rescinnamin, Reserpin, Spironolacton, Timolol, Trichlormethiazid, Benzthiazid, Chinetazon, Tricrynafan, Triamteren, Acetazolamid, Aminophyllin, Cyclothiazid und Merethoxyllin-procain sowie Gemische und Kombinationen davon enthält.

8. Zusammensetzung nach Anspruch 6, worin die pharmazeutisch wirksame Verbindung ein Bestandteil aus der Gruppe nach Anspruch 2 ist.

9. Zusammensetzung nach Anspruch 6, worin die pharmazeutisch wirksame Verbindung ein Bestandteil aus der Gruppe nach Anspruch 3 ist.

10. Ein Verfahren zur Herstellung einer Verbindung nach Anspruch 1, das folgende Stufen umfasst: Synthetisieren eines bicyclischen Lactams der Formel (VIII)

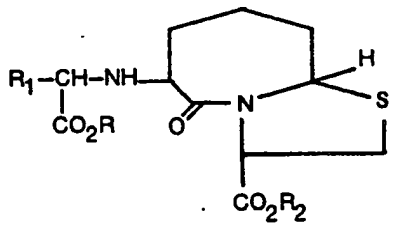


(VIII)

in der R_2 die vorstehen definierte Bedeutung hat, und anschliessend reduktives Alkylieren des Lactams mit α-Ketosäuren und -estern, anschliessend Entfernung von gegebenenfalls v rhandenen Schutzgruppen unter Bildung v n Produkt n der F rmel (I) und gegebenenfalls ls lieren des bi logisch aktiveren Diastere mer n durch Chromatographie oder Kristallisati n und gegebenenfalls H rst llen ein s pharmazeutisch verträglichen Salz s daraus nach herkömmlichen Verfahren.

Revendications

1. Un composé de formule (I)



(I)

dans laquelle:

R et R_2 sont indépendamment un hydrogène, un alkyle en C_{1-6}, un phényle, un naphtyle, un biphényle et les aralkyles correspondants ayant 1 à 6 atomes de carbone dans le fragment alkyle,

R_1 est un hydrogène; un alkyle ayant 1 à 12 atomes de carbone, un cycloalkyle ayant jusqu'à 12 atomes de carbone, un alcényle ayant jusqu'à 12 atomes de carbone et un alcynyle ayant jusqu'à 12 atomes de carbone; un alkyle en C_{1-6} substitué par un halogéno, un hydroxy, un carboxy, un alkylthio en C_{1-6}, un alcoxy en C_{1-6}, un (alcoxy en C_{1-6})carbonyle; un phényl-, naphtyl- ou biphényl-(alcoxy en C_{1-6})carbonyle, un amino, un alkylamino en C_{1-6}, un di(alkyl en C_{1-6})amino ou un alcanoylamino en C_{1-6} ou un aroylamino; un résidu de formule $R^A(CH_2)_n$—Q—$(CH_2)_m$ dans laquelle n est 0—2, m est 1—3, R^A est un phényle, un naphtyle, un biphényle un indolyle, un thiényle, un imidazolyle, un furyle, un benzimidazolyle, un pyridyle, un quinolyle, un isoquinolyle, ou un benzothiényle où les fragments aryles et hétéroaryles sont éventuellement substitués par un amino, un di(alkyl en C_{1-6})amino, un alkylamino en C_{1-6}, un hydroxy, un hydroxyalkyle en C_{1-6}, un aminoalkyle en C_{1-6}, un trihalogénoalkyle en C_{1-6}, un cyano, un nitro, un sulfonamido, un aroyle, un alkyle en C_{1-6}, un ou deux halogènes et un alcoxy en C_{1-6}, et Q est =O, =S, =N—R^B, —$CONR^C$—, —NR^CCO— ou —CH = CH— où R^B est un hydrogène, un alkyle en C_{1-6}, un phényle, un naphtyle, un biphényle, un aralkyle ayant 1 à 6 atomes de carbone dans l'alkyle et "ar" désignant un phényle, un naphtyle ou un biphényle, un alcanoyle en C_{1-6} ou un aroyle et R^C est un hydrogène ou un alkyle en C_{1-6}; un phényle, un naphtyle ou un biphényle où les aryles peuvent être substitués par un alkyle en C_{1-6}, un aminoalkyle en C_{1-6}, un alcoxy en C_{1-6}, un phényle-, naphtyl- ou biphényloxy, un aroyle, un hydroxy ou un ou deux halogènes; un aralkyle ou un hétéroaralkyle dont la portion alkyle contient 1 à 6 atomes de carbone et le fragment aryle et hétéroaryle est défini comme pour R^A, si bien que les groupes alkyles en C_{1-6} peuvent être substitués par un amino, un alcanoylamino en C_{1-6}, un aroylamino ou un hydroxyle et les groupes aryles et hétéroarylés peuvent être substitués par un ou deux halogènes, un alkyle en C_{1-6}, un hydroxy, un alcoxy en C_{1-6}, un phényl-, naphtyl- ou biphényloxy, un aroyle, un phényl-, naphtyl- ou biphénylthio, un amino, un aminoalkyle en C_{1-6}, un alcanoylamino en C_{1-6}, un aroylamino, un di(alkyl en C_{1-6})amino, un alkylamino en C_{1-6}, un hydroxy, un hydroxyalkyle en C_{1-6}, un trihalogénoalkyle en C_{1-6}, un nitro, un cyano ou un sulfonamido;

et leurs sels convenant en pharmacie.

2. Un composé de la revendication 1 qui est un constituant du groupe:

l'acide [3R-[3α,6α(S*),9aα]]-6-[(1-carboxy-3-phénylpropyl)amino]octahydro-5-oxothiazolo[3,2-a]azépine-3-carboxylique;

l'acide [3R-[3α,6α(S*),9aβ]]-6-[(1-carboxy-3-phénylpropyl)amino]octahydro-5-oxothiazolo[3,2-a]azépine-3-carboxylique;

l'acide [3R-[3α,6α(S*),9aβ]]-6-[[1-éthoxycarbonyl)-3-phénylpropyl]amino]octahydro-5-oxothiazolo[3,2-a]azépine-3-carboxylique, et

l'acide [3R-[3α,6α(S*),9aα]]-6-[[1-(éthoxycarbonyl)-3-phénylpropyl]amino]octahydro-5-oxothiazolo[3,2-a]-azépine-3-carboxylique.

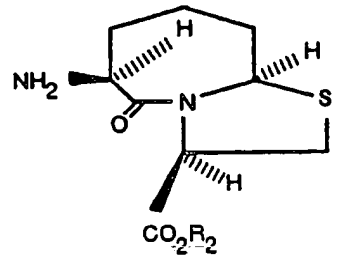
3. Un comp sé de la r vendication 1 qui est un constituant du groupe:

le [3R-[3α,6α(S*),9aβ]]-6-[[1-méth xycarbonyl)-3-phénylpropyl]amino]octahydr -5-oxothiazolo[3,2-a]azépine-3-carboxylate de n-butyle;

le [3R-[3α,6α(S*),9aβ]]-6-[[1-(éthoxycarb nyl)-3-phénylpr pyl]amino]octahydr -5-ox thiaz l [3,2-a]azépine-3-carboxylate d' 'thyle;

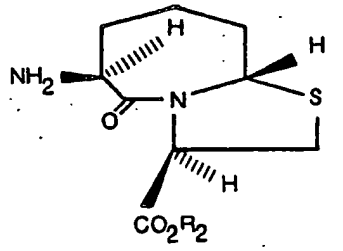
le [3R-[3α,6α(S*),9aα]]-6-[[1-(éthoxycarbonyl)-3-phénylpropyl]amino]octahydro-5-oxothiazolo[3,2-a]azépine-3-carboxylate d'éthyle;
le [3R-[3α,6α(S*),9aβ]]-6-[(1-carboxy-3-phénylpr pyl)amino] ctahydro-5-oxothiazolo[3,2-a]azépin -3-carboxylate d benzyle;
le [3R-[3α,6α(S*),9aβ]]-6-[(1-carboxy-3-phénylpropyl)amino] ctahydro-5-oxothiazolo[3,2-a]azépin -3-carboxylate de phényl;
le [3R-[3α,6α(S*),9aβ]]-6-[[1-(méthoxycarbonyl)-3-phénylpropyl]amino]octahydro-5-oxothiazolo[3,2-a]-azépine-3-carboxylate de n-butyle; et
le [3R-[3α,6α(S*),9aβ]]-6-[[1-(méthoxycarbonyl)-3-phénylpropyl]amino]octahydro-5-oxothiazolo[3,2-a]-azépine-3-carboxylate de benzyle.

4. Un composé ayant pour formule:



dans laquelle R_2 est un hydrogène, un alkyle en C_{1-6} un phényle, un naphtyle, un biphényle et les aralkyles correspondants ayant 1 à 6 atomes de carbone dans le fragment alkyle.

5. Un composé de formule



dans laquelle R_2 est un hydrogène, un alkyle en C_{1-6}, un phényle, un naphtyle, un biphényle et les aralkyles correspondants ayant 1 à 6 atomes de carbone dans le fragment alkyle.

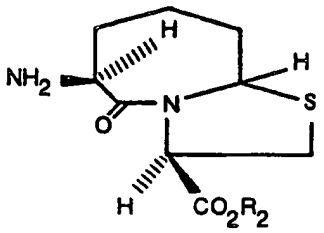
6. Une composition pharmaceutique utile dans le traitement de l'hypertension qui comprend un support acceptable en pharmacie et une quantité pharmaceutique efficace d'un composé de la revendication 1.

7. La composition de la revendication 6 qui comprend un autre antihypertenseur et/ou un diurétique choisis dans le groupe de l'amiloride, l'aténolol, le bendrofluméthiazide, la chlorothalidone, le chlorothiazide, la clonidine, l'acétate de crypténamine et les tannates de crypténamine, la déserpidine, le diazoxide, l'acide éthacrynique, le furosémide, le sulfate de guanéthidine, le chlorhydrate d'hydralazine, l'hydrochlorothiazide, l'hydrofluméthiazide, la métolazone, le tartrate de métoprolol, le méthyclothiazide, la méthyldopa, le chlorhydrate de méthyldopa, le minoxidil, le (S)-1-{[2-(3,4-diméthoxyphényl)éthyl]amino}-3{[4-(2-thiényl)-1H-imidazole-2-yl]phénoxy}-2-propanol, le polythiazide, l'ester pivaloyloxyéthylique de la méthyldopa, l'indacrinone et des rapports variables de ces énantiomères, la nifédipine, le vérapamil, le diltiazem, le fluméthiazide, le bendrofluméthiazide, l'aténolol, l'acide (+)-4-{3-{[2-(1-hydroxycyclohexyl)éthyl]-4-oxo-2-thiazolidinyl}propyl}benzoïque, le bumétanide, la prazosine, le propranolol, *Rauwolfia serpentina,* la rescinnamine, la réserpine, la spironolactone, le timolol, le trichlorméthiazide, le benzthiazide, la quinéthazone, le tricrynafan, le triamtérène, l'acétazolamide, l'aminophylline, le cyclothiazide, la méréthoxylline-procaïne, ainsi que leurs mélanges et leurs associations.

8. La composition de la revendication 6 dans laquelle ledit composé pharmaceutique efficace est un constituant du groupe selon la revendication 2.

9. La composition de la revendication 6 dans laquelle ledit composé pharmaceutique efficace est un constituant du groupe selon la revendication 3.

10. Un procédé pour produir un c mpos´ s lon la r vendication 1, lequel procédé comprend: la synthèse d'un lactame bicyclique de formule (VIII)



(VIII)

dans laquelle R_2 est comme défini ci-dessus, puis l'alkylation par réduction dudit lactame avec des α-céto-acides et -esters puis l'élimination des groupes protecteurs éventuels, pour fournir les produits de formule (I) et, si on le désire, l'isolement du diastéréoisomère ayant l'activité biologique la plus importante par chromatographie ou cristallisation et de plus, si on le désire, la préparation d'un sel convenant en pharmacie correspondant de façon classique.